Quality of life in multiple myeloma
Longitudinal trajectories and monitoring symptoms and quality of life to improve quality of care

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Quality of life in multiple myeloma: Longitudinal trajectories and monitoring symptoms and quality of life to improve quality of care

A thesis submitted to King's College London for the Degree of Doctor of Philosophy

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Abstract

Background: Multiple myeloma is an increasingly common disease, but there is little evidence about the change in symptoms and problems in more advanced stages.

Aim: To describe the health-related quality of life (QOL) trajectories in multiple myeloma, and to evaluate the longitudinal validity of the Myeloma Patient Outcome Scale (MyPOS), a questionnaire to monitor QOL and palliative care concerns.

Methods: A national, multi-centre, observational study comprising (1) a cross-sectional analysis merging data from two studies, and (2) a longitudinal study, recruiting patients at various stages of the disease. Demographic and clinical data was collected alongside QOL measures. Analysis: (i) prevalence of symptoms and independently associated factors with poor quality of life, (ii) latent growth mixture analysis of quality of life trajectories, (iii) longitudinal validity and reliability via Rasch analysis, Generalizability theory and responsiveness to change.

Results: (i) Cross-sectional study: 557 patients reported a mean of 7.2 symptoms with the most common symptoms, pain, fatigue and breathlessness, being present in 61-78% of patients. General symptom level, pain, anxiety and depression, physical decline, age and phase of illness had significant independent associations with high palliative care concerns.

(ii) Longitudinal study: Four classes of individual QOL trajectories were identified (n=224): declining HRQOL over 8 months, stable moderate to good QOL, improving QOL, and fluctuating poor QOL. Logistic regression analysis revealed general symptom level (OR = 1.28), pain (OR=1.03) and presence of clinically relevant anxiety or depression (OR=1.19) to be predictors for a declining or poor QOL trajectory.

(iii) The MyPOS demonstrated good to excellent test-retest reliability. Rasch analysis identified limitations of suboptimal scale-to-sample targeting, resulting in floor effects. Responsiveness analysis yielded an MID of +2.5 for improvement and -4.5 for deterioration.

Conclusions: People with myeloma have four main trajectories of QOL which can be predicted by symptoms and psychological concerns. These could be tested as triggers for additional palliative support. The MyPOS is a valid and reliable outcome measure to monitor these indicators in routine clinical practice.

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Other collaborations, contributions and output

Conference "Quality of life in multiple myeloma: recent international research and future developments". Conference organised on 31st March 2016 at the Cicely Saunders Institute, King's College London.

Abbreviations

ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
APCA	African Palliative Care Association
ASCT	Autologous stem cell transplantation
AUC	Area under the curve
CAT	Computer-adaptive testing
CI	Confidence interval
CML	Chronic myeloid leukemia
COSMIN	Consensus-based standards for the selection of health status measurement instruments
CRP	C-reactive protein
CSRI	Client Services Receipt Inventory
CTT	Classical test theory
DIF	Differential item functioning
ECOG	Eastern Co-operative Oncology Group
EMA	European Medicines Agency
EOL	End-of-life care
EORTC	European Organization for the Research and Treatment of Cancer
EQ-5D	EuroQOL 5D
ESAS	Edmonton Symptom Assessment Scale
FACT	Functional Assessment of Cancer Therapy
FDA	Food and Drug Administration
GEE	Generalised estimating equations

GMM	Growth mixture modelling
GT	Generalizability theory
HADS	Hospital Anxiety and Depression Scale
HIV	Human immunodeficiency virus
HRQOL	Health-related quality of life
HSCT	Haematopoietic stem cell transplantation
ICF	International Classification of Functioning, Disability and Health
IG	Immunoglobulin
IL	Interleukin
IRT	Item response theory
ISOQOL	International Society for Quality of Life Research
LGCA	Latent growth curve analysis
MDASI	M.D. Anderson Symptom Inventory
MDS	Myelodysplastic syndrome
MDT	Multi-disciplinary team
MGUS	Monoclonal gammopathy of unknown significance
MID	Minimally important difference
MM	Multiple myeloma
MNAR	Missing not at random
MyPOS	Myeloma Patient Outcome Scale
NCCN	National Comprehensive Cancer Center
NHS	National Health Service
NICE	National Institute of Clinical Excellence
POS	Palliative care Outcome Scale

PRO	Patient-reported outcome
PROMIS	Patient-Reported Outcomes Measurement Information System
QOL	Quality of life
RCT	Randomised controlled trial
RMSEA	Root mean square error of approximation
SCT	Stem cell transplantation
SEIQOL	Schedule for the Evaluation of Individual Quality of Life
SMM	Smouldering myeloma
SPC	Specialist palliative care
STAS	Support Team Assessment Schedule
TNF	Tumour necrosis factor
UK	United Kingdom
WHO	World Health Organization

1 Introduction

This study seeks to understand and compare the individual quality of life (QOL) and symptom trajectories of people with multiple myeloma over time and to explore the utility and acceptability of routine monitoring of QOL in this patient group.

In the past 40 years, QOL has evolved as a construct that is used frequently as an endpoint in health services research (1), to evaluate the effectiveness of treatments and therapies, to guide patient-centred clinical care (2) and to help decision-makers in allocating resources (3). Particularly in oncology and haematology, where therapies such as bone marrow transplantation, chemotherapy, surgery and radiation can have lasting powerful and toxic effects on patients' health, the study of QOL allows gauging the impact of the disease, treatment and side effects on the individual's wellbeing. Multiple myeloma, an incurable cancer of the bone marrow, is characterised by pathological proliferation of monoclonal plasma cells leading to anaemia and marrow failure (4). It is currently the third most common haematological malignancy (5,6) with 4,672 new cases diagnosed in the United Kingdom each year (7). As such, its impact on mortality and morbidity is high with an estimated average of 30 years of life lost in patients aged ≤65 (8). There is evidence that myeloma patients suffer from more symptoms and problems than patients with other haematological cancers (9). In addition, myeloma inflicts a high economic burden on individuals and society. Although it accounts for only a small percentage of all cancer types, cost for treating and managing the condition are among the highest compared to all cancers (10-13). As a consequence, measuring QOL alongside other patient-reported outcomes (PROs) in myeloma can help determine whether interventions and treatments are tolerable, acceptable, clinically beneficial and economically effective.

Information on QOL not only helps in determining the effectiveness of interventions and bringing the patient perspective into clinical and health research, it also has prognostic value and therefore helps to identify those at risk of developing future adverse outcomes such as treatment failure or death. Prognostic indicators help inform patients and doctors about the future course of the disease, especially about the risk of deterioration, and can help select those patients in need for treatment or supportive care (14). The prognostic value of health-related quality of life (HRQOL) for predicting survival has been shown in cancer (15-18), as well as chronic and life-limiting conditions, such as heart failure (19), HIV (20) and chronic kidney disease (21). Recently, the prognostic value of QOL in myeloma has been demonstrated in two studies (22,23). Dubois and co-authors (2006) (23) reported that quality of life changed consistently with the clinical response that patients experienced to bortezomib treatment and that a model of fatigue together with more traditional predictors like clinical toxicity, albumin and platelet count was able to predict survival.

Strasser-Weipl and Ludwig (2008) (22) demonstrated the prognostic power of psychosocial QOL for survival.

Despite the value that health-related QOL has demonstrated as an outcome, it is still rarely used in multiple myeloma. A recent systematic review found only 15 clinical trials that incorporated QOL as an endpoint (24). The main outcomes are response to treatment, time to progression, progression-free survival, duration of response, and overall survival (25,26). Despite myeloma being an incurable disease that places a high burden on patients and the health care system, and despite the existence of guidelines for supporting care (27) and guidelines for the use of PROs in haematology (28), PROs play a minor role in research and clinical practice.

One reason why QOL assessment is not used is that its added value for clinical practice has not yet been shown. This might be partly due to the fact that good quality information on how QOL develops throughout the disease trajectory is scarce. To date, only a handful of studies have measured QOL at several points in the myeloma trajectory (23, 29-36). These studies usually focus on people that participate in treatment studies of novel chemotherapeutical agents or bone marrow transplantation. Most of these studies are cross-sectional in nature. HRQOL is measured only at one point in time before, during or after treatment (30,32,34,36). Follow-up is usually limited. Not all people with myeloma are eligible for these treatments. Thus, these studies do not yield representative results. No study to date has looked at the impact of the advanced stages on people's well-being and needs.

The second reason why HRQOL measures are not used in clinical practice might lie in the fact that most questionnaires measuring this construct have been developed for research. Overly long measures with results that are hard to interpret for patients and clinicians hinder clinical applicability. Recent initiatives have focused on presenting information from QOL measures to clinicians and measuring the impact on communication in the clinical encounter (37). This has shown limited results. One avenue that remains under-explored is directly providing patients with the information from these measures via self-monitoring. It has been suggested that this could help patient empowerment (38). Some studies have explored the effectiveness of self-monitoring for detecting adverse effects of chemotherapy and problems in patients with lung cancer, prostate cancer or cancer survivors (39-44). However, it is not well understood how best to aid self-monitoring, how to feedback information in an appropriate way (39), and what measurement characteristics items need to have in order to allow tracking of individual changes.

Therefore, this study aims to address both gaps that have been identified – following a natural sample of patients with multiple myeloma at various stages of the disease over time to describe the trajectory of symptoms, psychological distress and HRQOL over time and during the advanced stages of the disease. It aims at identifying predictors for poor HRQOL to help target

services at those at risk of developing these adverse outcomes. The study will also explore which items perform well in monitoring individual changes in QOL and thus inform which measures can be used for application in routine clinical practice.

2 Background

2.1 Multiple myeloma

2.1.1 Epidemiology, clinical picture and disease course

Multiple myeloma is an incurable malignant type of bone marrow cancer arising from plasma cells, which form part of the immune system. In multiple myeloma these plasma cells become abnormal, proliferate and release only one type of paraprotein (usually immunoglobulin IgG, IgA, IgD, IgE) (45). IgG is present in 60% of cases, IgA in 20-25% and free light chain disease in 15-20% (4). Detecting this monoclonal immunoglobulin (M-potein) in the serum or urine usually leads to the diagnosis of the disease. The subtype free light chain disease is characterised by paraproteins accumulating in the kidneys, which causes kidney failure. The clinical features of the disease are in part determined by the rate of accumulation and the properties of the abnormal cells that are expressed (46,47). Myeloma belongs to the group of cancers known as plasma cell dycrasias, a heterogeneous group consisting of plasma cell leukemia, solitary plasmacytoma, chronic lymphocytic leukemia, malignant lymphoma, primary amyloidosis and others. Almost all multiple myelomas evolve from an asymptomatic pre-malignant phase, referred to as monoclonal gammopathy (MGUS) (48), or a more advanced premalignant stage known as smouldering myeloma (SMM) (49). MGUS and SMM progress to myeloma at a rate of 1% (50,51) to 10% (52) per year, respectively.

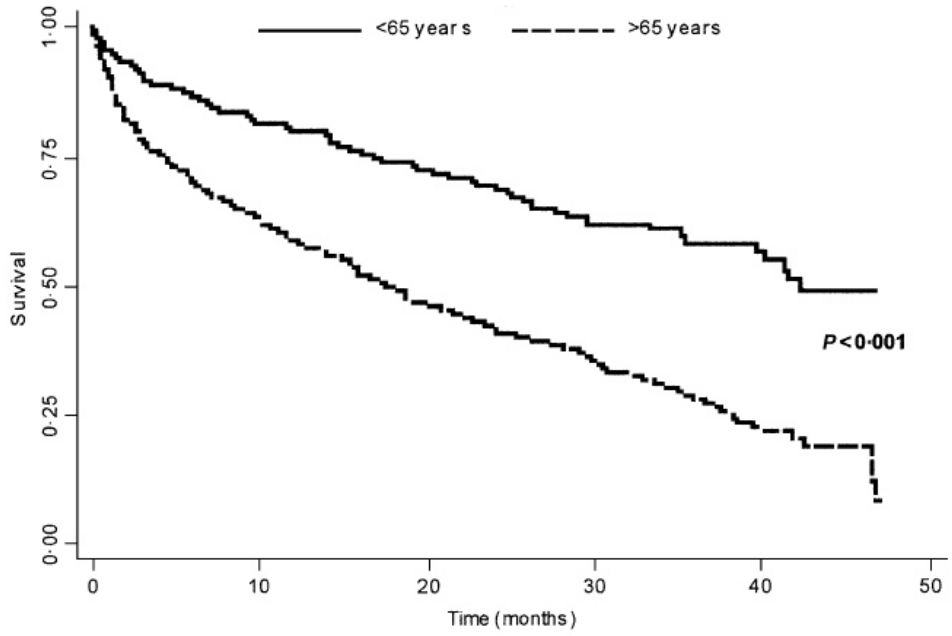
Multiple myeloma has unique features which sets this disease aside from other conditions. Myeloma usually presents with osteolytic bone lesions and their complications. Bone disease (destruction and remodelling) and bone pain are major causes of morbidity (53). Bone destruction may lead to hypercalcaemia and renal insufficiency. Other major clinical manifestations are anaemia and an increased risk of infection (54). Infection is the most common cause of death in this group. Treatment and management focuses on addressing these features and problems.

Multiple myeloma is currently the third most common haematological malignancy in the UK (5,6,55) and accounts for 1% of all cancers (56,57). Each year 4,672 cases are newly diagnosed. Incidence rates remain stable with 6.9 per 100,000 new cases in men and 4.5 per 100,000 cases in women (58). Nonetheless, there are more people living with myeloma which is related to the ageing of the population in recent years (59). The disease is more common in older age groups and age is considered a risk factor for the development of the disease (58). This has shifted the median age at diagnosis from 70 to 74 years (59,60). The disease is almost twice as common in Black African and Caribbean patients as in White patients (i.e. incidence rate of 13.1 per 100,000 in Black African men versus 6.7 per 100,000 in Caucasian men (58)).

Median survival has improved considerably in recent years with the introduction of high dose chemotherapy, novel agents and autologous bone marrow transplant (61,63). Median survival is about

5 years for younger patients and 18 months for patients aged 65 and older (45). This is because new treatment options (such as autologous stem cell transplantation (ASCT) which can result in a temporary complete response and prolong survival) mostly benefit younger patients (≤65 years) (8). Phekoo et al. (2004) (65) demonstrated differential survival rates for patients for those younger and older than 65 years in a population study in the South Thames region, using data from the Thames Cancer registry. They found a statistically significant difference of 24 months between these two age groups (see Figure 1, reprinted from (65)). The authors concluded that in order to improve survival and outcomes for patients diagnosed with multiple myeloma, treatment options and adequate planning of health care services needs to take into account the different profile of these patients, with added risk of complications arising from treatment and comorbidities (65).

Figure 1: Median survival according to age. Median overall survival in the group less than 65 years of age was 42 months and 18 months in the group aged 65 years and older (65).



The general goals of treatment include disease control, halting or reversing complications, extending survival and maintaining QOL (67-69). The extension of median survival time in multiple myeloma seen in recent years is largely attributed to more targeted therapies that result in a longer period of stable disease for patients, across all phases of treatment (70). Treatment approaches differ according to the group of active disease that the patient is experiencing. There are three categories: newly diagnosed (NDMM), stem cell transplant (SCT) and relapsed or refractory disease (RRMM) patients (71). Autologous stem cell transplant (ASCT), either in NDMM or as salvage therapy after relapse, is still the standard of care and first-line treatment for those under the age 65 (71,72). Increasingly, older patients are also transplanted, despite the considerable mortality risk associated with this procedure

(62). In ASCT treatment, patients receive induction therapy with either single or combination therapy of anti-myeloma agents, followed by maintenance therapy to prolong the period of complete or partial response (73-76). Especially lenalidomide maintenance has been shown to improve progression-free survival in younger (77,78) and elderly patients (79). The same is true for bortezomib (80). However, none of these strategies are recommended universally and therapy-related short-term and long-term side effects can curtail the length of maintenance regimens for patients (76,81). Transplant-ineligible patients receive combination therapy, consisting of 2-, 3- or 4-drug regimens usually containing melphalan and/or cyclophosphamide plus thalidomide or the new-generation drugs lenalidomide or pomalidomide (75,77,78,82). Disease response to these regimens is usually below that for transplant-eligible patients (66). For RRMM, most second-line and third-line combination chemotherapies are used until the refractory disease stage is reached. The choice of treatment is based on comorbidity profile, age, persisting toxicities from previous treatments and regimen-related toxicities (71). In general, at first relapse 40-82% of patients achieve a response and half of these will enter a second plateau phase. With each subsequent relapse, further lines of treatment have a lower chance of inducing remissions and the treatment-free interval will be shorter for patients (71). The duration of the treatment-free interval has been shown to affect QOL in patients with multiple myeloma (83).

Overall, the clinical picture together with the debilitating effects of various treatments show that QOL should be of primary concern to haematologists and their patients, especially given that multiple myeloma is still an incurable disease. Typical chemotherapy-related, short-term side effects entail nausea, vomiting, anorexia and diarrhoea (84,85), leukopenia resulting in general myelosuppression and immunosuppression with a large impact on social life and functioning in patients (84,85). Combined 3- or 4-drug regimens in particular yield more toxic effects than single agents (86-89). Some of these, particularly fatigue, anaemia, mood disorders and peripheral neuropathy, can have long-lasting effects on the patient's QOL (88). Although supportive care is a major part of treatment guidelines for multiple myeloma, supportive care needs in this population have traditionally not received enough attention, with depression and anxiety being undertreated (34,90) and fatigue, pain and nutritional problems only treated episodically (91-93). Supportive care has been defined as the multi-professional attention to the individual's multi-dimensional needs that should be available to all patients regardless of stage of illness or intention of treatment (94).

The focus of supportive care offered, however, seems to be narrower. The scope of therapies ranges from administration of simple drugs (e.g. bisphosphonates) to full, multi-professional survivorship care (94). In multiple myeloma, mostly the treatment of specific disease- and treatment-related complications is seen within the scope of supportive care. In guidelines, medication and surgery treatment for bone disease, infection, anaemia, thrombosis, polyneuropathy and pain as well as renal and cardiovascular toxicity is listed under supportive care (75,95). The 2011 UK guidelines as well as the National Comprehensive Cancer Network myeloma supportive care guidelines advise to manage

side effects using a mechanism-based, pharmacological approach, with a brief mentioning of non-drug methods (27,96,97). However, optimal comprehensive care in myeloma needs to consider the wider problems and impact that disease and treatment have on patients and their families, to improve the awareness and appreciation of HRQOL in both active and inactive disease (71).

Routine systematic assessment can help to monitor holistic needs. Although some of these approaches gradually play a more important role, current supportive needs assessment is confined to early myeloma stages (usually when patients enter their first treatment-free interval) (27,71). This might explain the generally low provision of palliative care in this population. This situation is also reflected in findings from studies that contrasted physicians' beliefs about patients' preferences regarding myeloma treatment with patient views (98,99). In one study, physician- rated mobility, side effects and effectiveness of treatment as the three most important attributes they thought that patients would value when making treatment decisions. This contrasted with patients' opinions who valued breaks in therapy over side effects and mobility. For patients, particularly periods of not having to think of the disease and therapies allowing them to lead a normal life with as little side effects as possible were chosen as most important attributes of therapy in MM (98). Aside from poor communication and a narrow focus of supportive care approaches, there are several other reasons why myeloma patients underuse palliative care services.

2.1.2 Palliative care and haematology

Despite significant advances in the treatment of multiple myeloma and other haematological malignancies in recent years, cancers like myeloma remain incurable with patients dying either from the disease, its complications or its treatment. Despite all myeloma therapy being considered palliative to an extent (95,100), the needs of these patients at the end of life and particularly in the dying phase have not been described. The bulk of epidemiological studies suggests that these patients do not receive specialist palliative care (SPC) services at the end of life (101,104). In order to create an interface between palliative care and haematological care, it is necessary to first identify and understand the barriers concerning access and receipt of palliative care services. This will allow recommendations regarding appropriate interventions to achieve a better integration (105).

Population trends in recent years have resulted in an increase in the number of people living with advanced, often multi-morbid disease in need of palliative care (106,107). The scale of the challenge requires system-level changes (108-110). This has led to a progressive increase of home palliative care programmes and other services (111), partly to achieve cost-effective end-of-life care outside the hospital (112) and partly meeting the preferences for dying at home (113,114). This population trend is also observed in those haematological malignancies mainly afflicting the elderly. Multiple myeloma is such an example (7,57,59,65). Although one recent studies demonstrated an increase in numbers of

referrals of haematological cancer patients to SPC services (115), the vast majority of studies point towards haematology patients remaining a distinct group in the hospital setting, with a high level of aggressiveness of care in the final days of life, increased use of technology and restricted carer access (101-103,116-121). Patients die on acute wards or in intensive care units (105,122,123). If referrals to palliative care occur, they do so very late in the illness trajectory (124-129). Furthermore, despite more than half of adult haematological patients eventually dying from their disease (130), palliative care and its role is poorly understood and integrated in this setting, partly due to the lack of evidence regarding the specific unmet palliative care needs in this group of patients (131-134).

In summary, studies demonstrate a lack of early and honest discussions regarding preferred place of death and dying, inadequate care of prevalent symptoms and problems, and high levels of patient and family distress (135). Already in 2003, the Nationale Institute for Clinical Excellence recommended the integration of palliative care and haematological services, as did other organisations (104,136,137). Possible factors that account for shortcomings of care at the end of life have been identified in few qualitative studies from Australia and the United States (102,138,139). Multiple patient-related, clinician-related and system barriers exist (125,129,140). Main barriers to introducing specialist palliative care at the patient level include a perceived lack of palliative care needs among patients, the potential for cure or life prolongation and heightened expectations regarding treatment outcomes. Also, uncertainty and rapid disease trajectories in which a clear end-of-life phase cannot be easily recognised result in a lack of prognostic models to indicate appropriateness of palliative care (103,139,141-143). Clinician-related barriers comprise low acceptability of palliative care, the stigma associated with palliative care or equating palliative care with end of life care, thereby using an inflexible model of curative versus palliative care, and lack of palliative care skills (103,139,141-144). System-level barriers include general funding shortages, organisation of care that precludes integration and the lack of randomised controlled trials to support early integration for patients with haematological malignancies (103,139,141-144). In the following chapters, five barriers will be discussed in depth.

2.1.2.1 Illness trajectory and characteristics of deaths in haematological malignancy

Haematological cancers are a unique and heterogeneous group with considerable variability in disease characteristics, features, and treatment pathways and outcomes (136). The WHO recognises over 60 different pathological subtypes (145). Especially the course of disease can vary widely, from aggressive and short trajectories to more chronic forms with frequent relapses requiring active treatment and management over a number of years (136). Even in the advanced haematological cancer population there is heterogeneity with profiles ranging from independent, ambulatory patients to those in intensive care units (146). This makes prognostication particularly difficult. Within single

haematological disease groups, certain subgroups exist. In multiple myeloma, older patients (usually over the age 75) (147,148) may not tolerate high-dose therapies and have an increased risk of therapy-related toxicities, resulting in shorter disease trajectories with different clinical features (149). Universally, haematological cancer patients experience unique complications like bone marrow insufficiency and chemotherapy-induced leukopenia (150). This leads to a high risk of infections that represent the major cause of death (123,132,137,151-153). In addition to the disease-related problems, further comorbid conditions and treatment-related side effects can enter the clinical picture and alter trajectories in the advanced stages (137). Significant symptom burden also arises from complications of bone marrow failure, e.g. fatigue, dyspnoea and bleeding, which can have a rapid onset and fluctuating course, especially in multiple myeloma (154).

Thus, the typical disease trajectory of myeloma and other haematological cancers differs from those in solid cancer patients. Cancer patients typically experience a prolonged period of preserved functional status followed by a period of marked decline during the last month of life (155-157). The disease trajectory in myeloma, on the other hand, may follow more that of chronic, organ failure diseases with intermittent periods of remission, relapse and the potential for sudden deterioration (145,152,158,159). These relapsing – remitting trajectories with a rapid onset of the dying phase create difficulties in determining the right time to engage specialist palliative care services and the transition to and involvement of such services is often left until late. This usually precludes care at home (105). In addition, haematology patients often require invasive care, such as transfusions and antibiotics, and may even in the advanced stages benefit from anticancer treatment (including chemotherapy and high-dose steroids) (123,143,151-153,160,161). These sudden and uncertain transitions are barriers towards the integration of palliative care, particularly if palliative care is perceived to follow curative approaches to care instead of trying the early integration of both paradigms (162).

2.1.2.2 Unpredictability and prognostic markers of end of life in haematology

In the advanced cancer setting, prognostication is one of the most important tasks for the planning of treatment and initiation of appropriate care approaches (163). In haematological disease, due to the non-existence of an easily identifiable phase of advanced disease, accurate identification of life expectancy and progression of illness has historically been a critical issue (164). The default system is non-standardised clinician's prediction of survival (163,165,166). However, this method is problematic because of its inherent bias towards overestimation of survival (167-170), leading to late referrals to palliative care and altering patients' expectations of treatment (171). Oncologist-driven referral is only one approach to the identification of patients in need of palliative care. Automatic referral, involving the use of predefined criteria relating to patients' diagnoses, prognoses and needs, is another approach. Several systems and triggers have been proposed (172-177), with some of them,

particularly Glare et al.'s (2011) (178) and Gomez-Batiste et al.'s (2013) (179) prognostication tools, having been empirically tested (180). In myeloma, decisions regarding treatment options are still subjective and largely based on the response to treatment, defined by the level of M-protein that can be detected after a course of treatment has been finished (26,181,182). Many prognostic factors have been proposed in myeloma, but none has been used consistently so far.

Among the most widely studied factors are biomedical variables, in particular albumin, haemoglobin levels, cytokines, and treatment response. Also, some comorbidity indices and their role in prognostication have been explored. Albumin and C-reactive protein, although proposed as general prognostic markers, have limited utility in multiple myeloma due to being confounded with disease processes such as osteolytic lesions (183). Anaemia and reduced baseline platelet count also have limited prognostic value since anaemia is multifactorial and partly sustained by concurrent chemotherapy and chronic disease (184,185). Cytokines, in particular interleukin (IL)-6, have been linked to disease activity in myeloma (186), and may be correlated with the duration of disease-free survival (187,188). A relationship between symptom severity and IL-6 (189) and inflammation processes (190) reinforces these results. However, whether IL-6 or other cytokines have good diagnostic characteristics to also indicate the advanced stage, when patients have potential needs for palliative care, remains to be investigated.

Currently, the majority of clinical predictions in myeloma care rely on a system that classifies the response to anti-myeloma treatment by evaluating the remaining amount of myeloma protein (26). Whether tumour response translates into survival benefits is an area of debate in the literature. Furthermore, its value as prognostic marker to indicate suitability for palliative care can be questioned. Tumour response, i.e. complete response, partial response, response duration and time to progression, as well as its linkage with biomarkers is not a useful substitute for patient outcomes (191). Particularly contested is the relationship between tumour response and QOL with some studies demonstrating a positive relationship and others not (192,193). Whether a responding patient experiences improvements in QOL is dependent on many additional factors not related to the biological response of the cancer per se. Although cancer progression is an important outcome, the need for palliative care relies more on the symptom and problem burden that patients experience, a burden that is not captured by these disease markers (23). Furthermore, the quality of response is also not a valid surrogate marker for survival (194), with particularly the depth of response (partial response versus complete response) not being uniformly related to survival time.

Acknowledging the situation that multiple myeloma and similar blood cancers show rising incidence due to the aging of society (6,59,60), prognostic indices for evaluating comorbidity in these cancer groups are now available. The Charlson Comorbidity Index (195-200), the Freiburg Comorbidity Index (201) and the Palliative Prognostic Index (202-204) have been used in conjuncture with the International Staging System (ISS) (205) for risk stratification in multiple myeloma (206-209). These

indices are composed of performance status assessments coupled with a weighting mechanism to preferentially weigh different comorbid conditions predictive of mortality, for example renal impairment and lung disease as in the case of the Freiburg Comorbidity Index (207-209). Prior studies have shown comorbidity's substantial impact on overall survival in several haematological cancers like myelodysplastic syndromes (210-212), acute myeloid leukemia (213,214) and in allogeneic stem cell transplantation populations (215). Some of these studies led to the conclusion that the presence of comorbidity can be more important than the disease itself in determining the advanced or dying phase (216). As these indices rely on the combination of comorbidity information with assessment of performance status, the role of performance status impairment as a possible prognostic factor for palliative care involvement needs to be determined. The Palliative Prognostic Index as well as the Palliative Performance Scale (203) have been shown to have good prognostic validity in the context of palliative care (217-219). However, these indices have only been tested in palliative populations which largely exclude haematological cancer patients. Since patients with multiple myeloma experience impairments in their physical functioning early on in the disease trajectory (7,220-222), the role of deteriorating performance status is questionable in this condition.

Some successes have been achieved in the use of QOL and symptom measures to predict survival in haematological cancer patients. Evidence is accumulating for the independent prognostic role of PROs for predicting survival in the advanced disease setting (223,224). Symptoms that have been found to be independently associated with survival are: fatigue (225), pain (226), dysphagia (16), appetite loss and anorexia (227), cough (228) and general symptom burden (229). One study in mixed haematological and solid tumour patients reported stage of illness and drowsiness on the M.D. Anderson Symptom Inventory as factors independently associated with survival in multivariate analyses (230). Similar results for overall symptom burden have been found in routine monitoring programmes using the Edmonton Symptom Assessment Tool (231-235). Wider domains of HRQOL are also related to survival, with physical functioning being among the most commonly evaluated indicators (224,225,236-240). Very little research of this kind has been conducted in haematological malignancies. However, data from three studies explored relationships of QOL and survival in multiple myeloma (see Table 1).

Table 1: Overview of prognostic factor studies of PROs in patients with haematological disease (based on (241))

Study	Population	Sample size	PRO questionnaire	Survival predicted by
Strasser-Weipl & Ludwig (2008) (22)	MM	92	EORTC QLQ-C30	Role, emotional, cognitive and social functioning
Dubois et al. (2006) (23)	MM	114	FACIT-Fatigue	Fatigue
Wisloff et al. (1997) (242)	MM	468	EORTC QLQ-C30	Physical functioning

Descheler et al. (2013) (243)	Elderly AML and MDS patients	195	EORTC QLQ-C30	Fatigue
Oliva et al. (2011) (244)	Elderly AML patients	113	EORTC QLQ-C30, QUAL-E	Physical functioning, functional well-being
Efficace et al. (2012) (230)	Mixed (MDS, NHL, AML and MM)	108	MDASI	Drowsiness
Jerkeman et al. (2001) (245)	Lymphoma	92	EORTC QLQ-C30	Global QOL

Abbbreviations: MM: multiple myeloma, AML: acute myeloid leukemia, MDS: myelodysplastic syndrome, NHL: Non-Hodgkin lymphoma, PRO: patient-reported outcome measure, EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire –Core30, FACIT: Functional Assessment of Chronic Illness Therapy, MDASI: M.D. Anderson Symptom Inventory, QOL: quality of life

These studies point towards the potential role of PROs, particularly inventories combining symptoms with QOL domains, to provide indicators for the appropriateness of palliative care involvement.

2.1.2.3 Unclear goals of care

Advances in treatment options and new therapies tested in clinical trials frequently lead to overoptimism in haematologists regarding potential success of treatment in patients. One main concern of haematologists regarding early referral to palliative care is the fear to create confusion with respect to treatment goals. This might upset patients and families (105). However, this view loses sight of the fact that in multiple myeloma, essentially all treatment is given with a palliative intent (100). The intended goal of extending survival can compound the difficulty of re-examining situations of declining health (246). Moreover, advance care planning and discussions regarding preferences of care are often performed late (247). However, the absence of any plans to manage the wider physical and psychosocial distress arising from the cancer and its treatment result in the patient not being prepared for the possibility of progressive disease. This prevents patients to receive appropriate end-of-life care (248). Advance care planning, the process of communication between clinicians, patients and their families regarding wishes and preferences for care in the advanced and dying phase (249), is an understudied area of research in haematological disease. The only available evidence is for those undergoing haematopoietic stem cell transplantation (250-252). However, advance care planning is beneficial and desired in this group of patients and should be extended, particularly with regard to the unpredictable course of haematological disease and multiple myeloma in particular (253-259).

2.1.2.4 Attitudes towards palliative care and lack of knowledge of palliative care

The misconception that palliative care is only for patients at the end of life is a particularly strong barrier among haematologist for referral to palliative care (260). Several studies, mainly in the

Australian and US contexts, have shown differences in the conception of palliative care in solid tumour oncologists and haematologists. A study surveying attendants of a national oncological conference reported a higher proportion of oncologists referring patients early to palliative care than their haematologist colleagues. Reasons for non-referral being cited were wishing to control the disease process, the fear of creating the wrong conception that the haematologists had given up on the patient, or an inability to see how palliative care could benefit haematological patients with specific symptom control needs (162). Similar results were found in a mixed methods study exploring differences between the specialties in referral patterns (261). Haematologists emphasised different treatment goals, chemotherapy and preference for controlling palliative aspects of patient care themselves as the main barriers to a joint model of care (261). Although haematology care, like all fields of medicine, has the potential to offer generalist palliative care to its patients, the philosophical orientation towards cure may lead physicians and nurses in this setting to being more willing to accept a poor QOL and high symptom distress during intensive treatments, particularly HSCT or chemotherapy (262,263). The resistance to palliative care may result in unnecessary suffering of the patient and his or her family, as pointed out by McGrath and Holewa (158) who cited attitudinal barriers among the most important for the lack of integration.

Another factor in the low utilisation of palliative care services among haematologists is the lack of awareness of what palliative care is, when it is appropriate to transition a patient to services and the possibilities of early integration and co-management (105). Hui and colleagues (2015) surveyed second year oncology fellows regarding their experiences of fellowship training and identified a lack of skills with regard to symptom management and advance care planning/communication (264). Another study by the same group showed that haematology specialists preferred the term supportive care over palliative care and the change in label to supportive care was perceived to result in higher proportions of newly diagnosed patients being referred (265). The lack of knowledge about palliative care in this group is probably linked to the lack of standardised referral criteria and the lack of evidence around optimal transition points and the effectiveness of co-management models of care (105).

2.1.2.5 System barriers to the integration of palliative and haematological care services

Partly, these barriers are related to structural problems within healthcare. Difficulties in the referral process include shortage of hospice beds and the high intensity of medical support that can preclude – at least in the American context – a referral to hospice services for haematological patients (150). Integration would also be aided by joint models of care being anchored into the delivery of care on a structural, organisational and policy level (161).

Palliative care focuses on achieving the best possible QOL at the same time as curative or life-prolonging treatments (143). According to the new definition of the WHO (266), the active and multidimensional care of the patient and their family can integrate from point of diagnosis and continue during phases of remission to the end of life (and beyond, in the form of bereavement care). The palliative care philosophy emphasises that it is not the prognosis that determines suitability. Rather, unmet palliative care needs should determine who receives palliative care (90). Palliative care is further characterised by an interdisciplinary approach with the goal of providing care for all multidimensional problems (e.g. physical, psychological, social, spiritual or practical) (267). Benefits of palliative care have been demonstrated, including improvements in QOL (172,174), improved symptom management (268), diminished aggressiveness of care at the end of life (172,269,270), enhanced ability to meet preferences for place of care and place of death (271), reduced cost (269,272), and even improved survival (172). The improved survival observed in a study providing early outpatient palliative care to newly diagnosed patients with advanced non-small-cell lung cancer was possibly related to the avoidance of hospitalisations, better symptom management and treatment of depression in the last weeks of life (270). This evidence demonstrates that the earlier introduction of palliative care in the disease process can address some of the challenges around prognostication identified as important barriers for haematological cancer patients (132,273).

At a basic level, early integration is influenced by the model of care, particularly by how well palliative care is embedded into oncology practices (274). A systematic review found different models of integration, ranging from simple linkage to coordination and full integration achieved when resources from oncology and palliative care were combined (275). Indicators for integration of palliative care with haematology could be the existence of interdisciplinary palliative/haematological teams or combined tumour boards, a simultaneous care approach, routine symptom screening, and palliative care guidelines and pathways (275). In multiple myeloma care, early integration of SPC could yield potential benefits through management of side effects and symptoms, longitudinal psychosocial support for patients and their families, and early conversations about preferences for care, prognostic understanding and advance care planning (276). However, fully integrated models of care are yet to be developed (143,277).

Over the last few years, several organisation have called for the early integration of palliative care in oncology or haematology and specified guidance documents (278,279). Although recent haematological clinical guidelines recommend that palliative care clinicians have central roles in haematological care teams (136), only few initiatives have tested innovative models of care (135). Some pilot projects established palliative care services on haematopoietic transplant units in hospitals and found that this early introduction did not shorten survival or dismiss hope in patients but appeared to improve symptom burden (132). A small randomised controlled trial tested the home provision of pamidronate to patients with multiple myeloma and found a small but not statistically significant trend

in favour of home treatment (280). Another qualitative study provided blood products at a day hospice and explored patients' views on this procedure. The majority of patients was in favour of receiving transfusions at the hospice day unit, mainly due to better access and parking facilities at the hospice (281). The only study that tried to establish a full palliative home care service for haematology patients in Italy reported a higher rate of home death and less hospitalisations at the end of life (282). However, since the pilot study included only 15 patients, the generalisability of the findings is a concern.

Overall, the integration of palliative care and haematology remains an underdeveloped field. Current models of SPC provision and end-of-life care services are not geared towards supporting haematological patients. Numerous barriers, particularly around prognostication and attitudes towards palliative care, need to be addressed. Early integration and a paradigm shift towards standardised monitoring of symptoms and palliative care problems could help identify patients earlier in their disease trajectory.

2.2 Quality of life and multiple myeloma

2.2.1 Definition and model of quality of life in multiple myeloma

With improvements in treatment and care for patients with myeloma the exploration of the impact of the disease on QOL becomes important. The field of QOL and health status assessment is relatively young. In the 1970s, the first generic assessment tools were developed (283). Prior measurement of patient-related variables was largely limited to measures of functional ability (e.g. Karnofsky Performance Scale (284)) that were taken to represent QOL (285). The term QOL was indexed in Medline in 1975 and since then the number of QOL publications has risen exponentially (286). Traditional endpoints in clinical trials assessed survival or progression-free survival, but gradually HRQOL has been introduced as a secondary outcome to inform treatment decision making in all health care and in multiple myeloma (285). After the introduction of the guidance on incorporation of patient-reported outcomes issued by the Food and Drug Administration in the US (287), the percentage of trials with secondary HRQOL endpoints has grown dramatically from 25% up until 1994 to more than 75% currently (288).

However, despite QOL permeating medical effectiveness research, the study of QOL is limited by a plethora of definitions of the term, which has led to the perception of QOL being an amorphous concept (289). Definitions of QOL within healthcare can be classified into three groups, based on their scope – definition that see QOL as a part of health care (290), definitions of QOL that look at the impact of illness on the individual (291), and definitions of QOL as a multidimensional construct

consisting of numerous domains important to the life of the individual (such as physical, psychological, social and spiritual wellbeing (292)). One of the most widely used definitions is the one by the World Health Organization (293). It states that quality of life is defined

> *"as [an] individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns. It is a broad-ranging concept affected in a complex way by the person's physical health, psychological state, level of independence, social relationships, and their relationships to salient features of their environment." (p.1404)*

This definition recognises the subjectivity of QOL – it can only be understood from the patient's perspective. It also indicates that an appropriate assessment can only be made by asking the person directly (294). The WHO definition also recognises the broader world individuals live in and the importance of assessing these wider domains. This is contrary to narrow definitions of HRQOL that focus solely on the effects of illness and treatment and do not take into account non-health related aspects (295). HRQOL has also traditionally been associated with a pathology model of health. HRQOL usually focuses on impairment in physical function and mental decline, an approach that disregards the dynamic nature of QOL (289). Following the WHO definition, values and expectations play a major role in making an assessment of QOL and wellbeing. This is in line with one of the earliest recognised definitions of QOL by Calman (296), who saw QOL determined by the gap between an individual's hopes and expectations and the reality. The assessment of QOL can therefore change when individuals adapt to an illness or an event in their life (34,297-299). The subjectivity inherent in the term is sometimes perceived to render outcomes like QOL, in comparison to seemingly objective parameters like biomedical variables, less robust (300).

The two definitions cited above define QOL as a term belonging to the individual. There is also a large philosophical debate about the societal, objective perspective of QOL and health and how the well-being of whole nations can be captured in routinely collected indicators (301). These definitions are well beyond the scope of this thesis. However, it demonstrates that QOL is often used as a generic label or an umbrella term to cover a variety of concepts (302). Ferrans has proposed a taxonomy of definitions and conceptualisations of the term in the early 1990s. She defined six broad categories (303-305): normal life, social utility, happiness, satisfaction with life, achievement of personal goals and natural capacities. The taxonomy has since been extended to include utility, the preference-based health state evaluation common in economic analyses within treatment effectiveness research, and satisfaction with specific domains of life (306,307). Most QOL assessment tools occupy the middle range of collecting information on a broad array of domains hypothesised to be related to or indicate the level of QOL that is experienced by the individual (308).

Depending on the conceptual model and the definition of QOL followed, measurement approaches can differ considerably. Although multidimensionality is mapped in most measurement theories, assessment instrument vary regarding the number of domains that are encompassed by the measure. The usual consensus regards physical, emotional, social, role functioning and overall QOL as the core domains (309). Depending on the instrument, core or disease-specific symptoms (as is the case mostly in disease-specific measures such as the EORTC QLQ-MY20 (221,310)) can complete the picture. Recently, the inclusion of existential and spiritual domains has been advocated (311). The coverage and comprehensive composition of measures is of importance when the clinical utility of these measures is concerned. A few distinctions play an essential role, particularly the distinction between the terms health-related quality of life and QOL or well-being, and the distinction between health status and health evaluation measures (295). HRQOL, as defined by some authors, equates with impairment and disability. The term is rooted in the tradition of functional assessment like in Karnofsky's performance scale (284). It focuses on those aspects of life that can be affected by medical treatment, in particular functioning and role performance (312). As such, it does not represent QOL which is understood to be more consistent with well-being and reflect satisfaction with life and level of mood (313). Covinsky et al. (1999) (314) have shown that health status and QOL are distinct constructs (314,315). The assumption that a fully healthy life is identical with a high QOL can thus be challenged. The paradox of good QOL in the presence of significant health problems or even in the presence of very advanced disease makes this distinction the more pronounced (316,317).

The second large distinction within QOL measurement is between measures that assess the status versus those that ask an evaluation of a problem from an individual (295). The WHO definition of QOL (293) that was referred to above shows both aspects – it asks for the individual's perception of their position in life, which is a question of perceived status, but then asks how this corresponds with the individual's standards, goals and expectation, which constitutes an evaluation. The wording within QOL definitions and conceptualisations as well as measurement tools is distinct in these groups. A status measures usually asks about the severity or the extent of a problem. Questions about how distressing a symptom or problem is or how much the individual is bothered by it are two typical wordings for evaluation measures. These distinctions matter as scores can differ markedly between the two types of measures even though measures may assess the same domain. Moderate to small correlations have been found between the SF-36 (health status) and the Quality of Life Index (health evaluation) in patients with HIV/AIDS (318) and between the EORTC QLQ-C30 and the FACT-G (319).

The multidimensionality, subjectivity, and dynamic nature of the construct and the lack of a consensus as to its definition have led research into QOL to be perceived as 'atheoretical' (311). Fayers and Machin characterised QOL as an ill-defined term (320). No definition to date has identified the essential elements and characteristics of QOL (307). There is an abundance of conceptualisations, yet

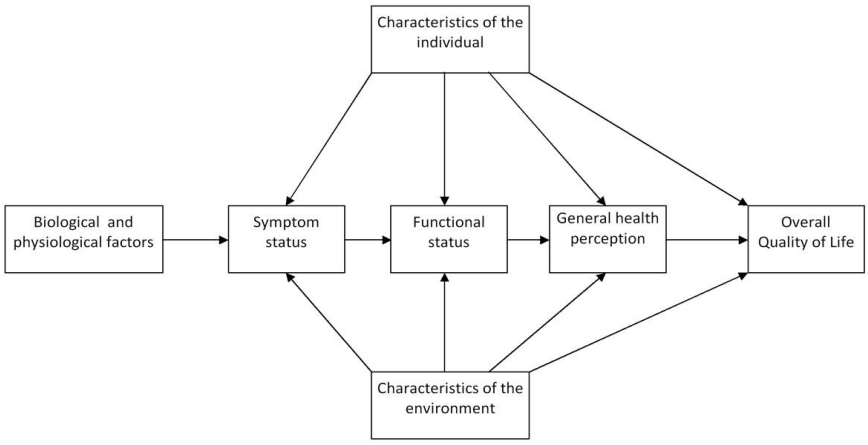
also a lack of debate as to a consensus (311). A review reported that at least 25% of authors of QOL publication did not define the term per se and a distinction between factors that may influence QOL and those that may reflect QOL was not made in half of the reviewed literature (321). The non-universal inclusion of domains further renders QOL results incomparable (322-325). Conceptual models that guide research are needed to place QOL and its related concepts in a context and model the inter-relationships among them. A theoretical model or framework is defined as a model that includes the structure of the elements and their relationship within a theory and hence allows the formation of hypotheses about pathways and relationships among elements (326). A theoretical framework can thus enable conceptual clarity and make the term QOL useful within clinical practice. QOL research then is used to identify the causes of variation and how these can be altered. From such a theory, guidance on how to intervene and improve QOL or its aspects can be gleaned (327). It further links health outcomes with health care services and how decrements in QOL may translate into specific supportive care needs (328).

Two systematic reviews have specifically identified those models of QOL that have been used in a health-related context. Bakas et al. (2012) (329) found that among models, Wilson and Cleary's model of QOL (330) was the most widely used, alongside its revision by Ferrans and colleagues (303,331). The second most common model was the one by the International Classification of Functioning, Disability and Health (ICF) (332,333). This result was also confirmed by Taillefer and co-authors (321). These models define the domains that make up the concept and hypothesise causal relationships among these domains (330,334-336). Conceptual models of QOL can be classified into several categories (295,337), of which the three most important types of model are: mediated models, interactive models and adaptation models (295).

a) Mediated models

In this category belong models which hypothesise direct relationships among their elements. Wilson & Cleary (330) propose a model that links biological and physiological variables to QOL and its antecedents via a direct pathway (see Figure 2).

Figure 2: The Wilson & Cleary model of QOL (330)

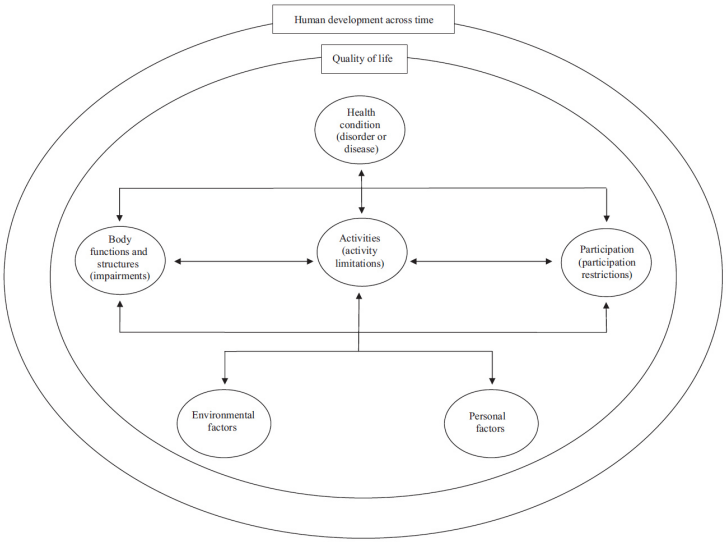


Thus, fully mediated relationships exist among the variables that influence QOL. Biological and physiological variables only have an indirect impact on QOL via affecting symptom status which then affects functioning. Functioning in turn only has a mediated effect on QOL via general health perceptions. In recent years, researchers have begun to use these causal models for investigating HRQOL, but also to study whether the relationships between domains hypothesised in the model hold true when applied to oncological patients or populations with chronic or life-limiting conditions (315,338-341).

b) Interactive models

The ICF proposed a partially mediated model that allows for direct and indirect links between constructs. The conceptual model posits bidirectional links between body function and structures (i.e. symptoms that lead to impairments), activities (limitations in physical function, self-care, carrying out daily activities), and participation (i.e. restrictions in role and social functioning) (332). All three concepts can directly influence the outcome HRQOL or indirectly influence it by affecting one of the other elements. This model, like the Wilson and Cleary QOL model, also presumes an influence of more distal personal and environmental factors. These variables can only impact on the health condition by influencing one of the elements body function, activities or participation. The model is in line with the WHO's definition of QOL (293). McDougall et al. (2010) (333) have proposed a modified version of the ICF model that includes QOL and contextual factors (see Figure 3).

Figure 3: Modified version of the ICF model (taken from (333))



c) Adaptation models

Adaptation models are all mediational models as they hypothesise influences or mediators that determine perceived QOL (289). These mediators are cognitive appraisal processes such as mastery, self-efficacy, perceived control over life and other cognitive processes (334). These models try to further characterise what was termed a general health perception in the model by Wilson & Cleary (330). One of the most prominent models is one linking stress, coping and adaptation theories and emphasises the relationship between the person and its characteristics and the environment which acts as a stressor (342), based on Lazarus & Folkman's theory of stress and coping (343). Other examples of adaptation models are Zissi et al.'s model of QOL developed in individuals with severe mental health problems (334), and Sprangers & Schwartz's model of adaptation/response shift (344).

Of these models, the model by Wilson & Cleary (1995) (330) is the most widely used (321). This might be because the authors defined the levels contributing to QOL as the natural progression of assessments within health care. Biological factors, treatment status and clinical signs are directly observable by the clinician or can be measured in clinical tests. Functioning is assessed either by the patient or the clinician through self-report or standardised performance tests. The components that are more proximal to overall QOL, particularly general health perceptions and other mediating variables (e.g. adaptation processes), can only be assessed and reported by the patients themselves, making use of PROs. In fact, symptoms (the second distal element of QOL) also falls into this category. The model presents two levels of empirically testable hypotheses. One is about the sequence of elements which directly translates into the amount of correlation they might show to the outcome overall QOL. The second range of hypotheses relates to the mediation of elements within the model. The model indicates that more proximal elements are subject to greater mediation by personal and environmental characteristics (345). This has consequences for how measures of QOL consisting of these domains

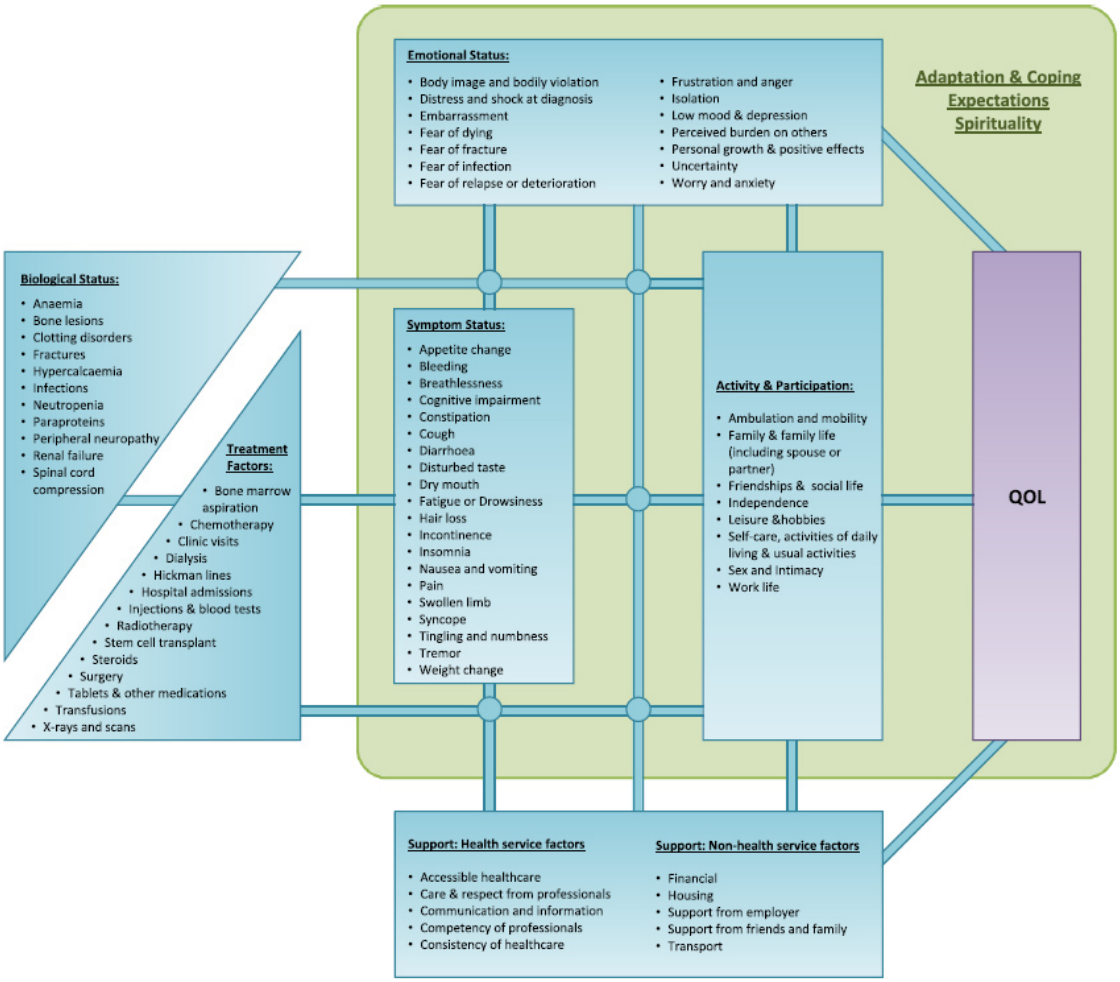
can be used in clinical research and practice. First, the more proximal the measure to overall QOL, the smaller the effects from disease and treatment will be. This can also be an explanation for why ceiling effects are reached in measures. Furthermore, treatment will yield greater results the more severe the symptoms are in a patient (346). Empirical tests, usually in the form of structural equation modelling, have provided strong support for the model in a variety of illnesses, ranging from chronic conditions to potentially life-limiting illnesses and cancer (338,347-354). Some problems with the unidirectional sequence of elements have been identified early on, which led to a revision of the model by Ferrans and co-authors (331). They allowed bidirectional relationships between the elements leading to QOL and allowed mediating factors to also influence biological factors.

Fayers (340) critiqued the model with regards to the complexity of relationships that are posited between the elements. How each element should be operationalised is not clear. He also points out that an important distinction is lacking in the theoretical model. Fayers and co-authors (1997,2002) (339,340) introduced the distinction between reflective/indicator and formative/ causative variables within a QOL framework. In a reflective model (355), variables or items in a questionnaire reflect the QOL level of a person. Causative variables are variables that directly cause or influence QOL. For example, a low QOL that leads to psychological distress, anxiety and depression may reflect the level of QOL (indicator variables), whereas the symptoms and functional limitations may have caused the low level of QOL in the first place and are thus causal variables (356). These distinctions need to be made clear in the arrows that link the boxes and also in how the respective variables are handled in the regression and factor analyses in psychometric validation.

Which model performs best in multiple myeloma is currently unknown. The subject of how QOL is perceived and constructed as well as affected by influencing variables has only recently been studied in three qualitative studies. To date, there is no empirical test of different models of QOL in this disease or in the wider haematological literature. Osborne et al. (2014) (357) in a study using 40 semi-structured interviews and two focus groups, asked patients with multiple myeloma how they would define QOL, what elements brought quality to the individual's life and how myeloma had impacted on their QOL. Partly due to the health-related focus of the interview questions, participants raised over 80 issues mainly related to their health. The resulting model that represents the relationships between overall QOL and its elements was eventually proposed to follow Wilson & Cleary's model (330) (see Figure 4). Similar to this model, participants in the study perceived biological status, treatment factors and symptom status as less closely related to overall QOL. Moreover and in contrast to Ferrans' revision (303,331), participants indicated a strong causal relationship of biological and treatment factors only if they led to symptoms which led to impairments in the subsequent elements of functional status and health perceptions (357). A difference to Wilson & Cleary's original conceptualisation was observed in the role of general health perceptions, in particular expectations, adaptation & coping and spirituality/religiousness. Other than only influencing the perception of

functional status to QOL in a mediating mechanism, adaptation or spirituality formed the essence of QOL in some patients, thus acting as a reflective variable according to Fayers' theory (339,340,351,356). Furthermore, health service factors and the satisfaction with received care were mentioned as directly influencing QOL, a further adaptation and new finding that led to a revision of Wilson & Cleary's theory (357) (see Figure 4).

Figure 4: Theoretical model of the QOL of people with multiple myeloma (357)



Two other studies aimed to depict relationships between QOL and its elements. Baz et al. (2015) (358) elicited some specific impact of symptoms (particularly side effects of treatments) on daily activities, work, family and leisure activities and independence in myeloma. Similar to Osborne et al. (2014) (359), they described a direct impact of clinic visits and quality of care on HRQOL. In contrast to the Wilson & Cleary model, however, a direct influence of the disease not mediated through aspects of functioning was allowed, as was the direct influence of symptoms onto HRQOL. The model further did not distinguish between reflective and causative indicators (358). A similar situation arises in Zabora et al.'s model (360). Their study used expert and patient consultation for the derivation of guidelines for supportive care and thus does not constitute a genuine qualitative study. Rather than proposing a model that universally depicts the relationships between the elements influencing and reflecting QOL, the authors focused on mapping the temporal sequence of specific problems and how these influence QOL at different stages of the disease (360). The stages were defined as relating to treatment and ranging from diagnosis of pre-forms of myeloma over newly diagnosed patients to remission, first relapse, and subsequent relapses into refractory disease (360). Their model constitutes

a conceptual rather than a theoretical framework and the authors fail to define the nature of relationships between the elements in the model. For subsequent QOL measurement development this poses a problem in deriving items for a QOL measure.

To conclude, any research into quality of life should be clear about its definitions and the underlying conceptual or theoretical model that guides the research (307). Researchers need to distinguish between indicators and determinants of QOL (339,340,351,356). Little is known about whether the hypothesised interactions and relationships in the models hold true generally and specifically in real-world samples of myeloma patients and whether these proposed interactions are an accurate representation of the interrelationships. Research into QOL therefore should clearly identify the theoretical model that guides the research and, if possible, try to test the hypothesised relationships among the constructs. In this PhD study, Osborne et al.'s definition and model of QOL in multiple myeloma is followed, with hypotheses regarding the differential influence of factors onto QOL being derived from the model (357). In the next section, literature regarding the symptom burden, QOL-related problems and the longitudinal trajectories in multiple myeloma will be reviewed to provide a more fine-grained picture of the problems experienced by patients.

2.2.2 Symptom burden and quality of life in multiple myeloma

The clinical picture of multiple myeloma is that of a condition that presents with multiple debilitating symptoms and problems. These are either caused by the disease itself (like bone pain, infections, renal failure), are associated with treatment (like intensive chemotherapy, stem cell transplantation, maintenance therapy) or with side effects of these treatments (71). Patients are aware that the disease cannot be cured and will ultimately return, progress and lead to further problems and disabilities. In a qualitative study of patients living with relapsed myeloma, participants characterised the disease experience as living with uncertainty and enduring it (361). Dependent on the physical impact the disease had on their life and the coping mechanisms they used, patients were more or less able to adjust to this state of not knowing and not being able to plan the future due to the prospect of deterioration and living with the inevitability of relapse.

Thus, the disease and its treatment have a profound impact on QOL. Despite the push within oncology to incorporate PROs and a patient-centred view in clinical trials and clinical decision making (287,362,363), HRQOL is not yet routinely assessed in myeloma clinical practice and research. A systematic review assessing the impact of HRQOL measurement on clinical practice in myeloma identified only 15 clinical trials published between 1996 and 2008 that used this outcome (24). The fact that HRQOL does not play a role in clinical practice is further supported by official guidance for outcome evaluation in phase III trials in myeloma (25,26). Evaluation of the benefit of new therapies

focuses on prolongation of survival and the progression-free interval and response to therapy only (26).

Only since 2010, attempts have been made to understand what these response categories mean in terms of patient experience. Ancaster et al. (2013) (83) examined how the treatment-free interval and its duration impacted on HRQOL. They showed that patients had better HRQOL during their first treatment-free interval (as opposed to treatment-free intervals after second line or third-line treatment) and that the length of the interval was associated with HRQOL (83). This is the only study so far in which the relationship between HRQOL and response has been studied in a nationally representative sample (364-366). Almost all information on HRQOL in myeloma is treatment-specific and does not reflect the treatment course or the whole disease trajectory (23,24,32,367). It is not apparent which factors of the disease and its treatment have the most impact on QOL and whether this impact changes when patients with myeloma enter a new phase in their disease (for instance the relapsed/progressive phase) (368).

There is some evidence that people with myeloma suffer more symptoms and problems than those with other haematological cancers like leukemia and malignant lymphoma (9). The 45 patients in a cross-sectional survey of 470 haematological cancer patients in Denmark reported 5.6 symptoms on average, of which 2.3 were rated severe. They also reported the highest levels of pain, fatigue and constipation as well as limitations in role, physical and social function (9). The fact that myeloma patients have poorer QOL than the general population with severe symptoms and impairments in functioning was also demonstrated by Gulbrandsen et al. (2001) (32). To date, only a handful of studies have measured QOL at several points in the disease trajectory (23,29-36). These studies usually focus on people that participate in treatment studies of novel chemotherapeutical agents or that receive bone marrow transplantations. Most of these studies are cross-sectional in nature (30,32,33,36).

Related to QOL is the assessment of the supportive care needs of this disease group. Only one study to date has assessed these needs in a sample of 134 patients living with myeloma (on average 5 years post diagnosis) (90). Unmet supportive care needs mainly centred on accessibility of health care services and information needs. The study also found moderate levels of QOL, with the most affected areas being physical, role and emotional functioning, pain, fatigue, dyspnoea, appetite loss, insomnia and constipation (90). However, it is unknown how these needs progress when patients enter the more advanced stages of the disease. As shown above, palliative care services are currently not provided to myeloma patients, despite existing guidelines (27,86). Areas of further research need to address the following gaps in the evidence (105,132): (a) identifying and describing the symptom patterns and levels of distress at different points during the illness trajectory, (b) describing the multidimensional needs and QOL-related problems of patients and carers, (c) charting the course of QOL during the

whole disease trajectory, and (d) determining preferences of patients and family carers for end-of-life care.

Describing symptom patterns in multiple myeloma, understanding how QOL and QOL-related problems change over time and which factors are related to poor QOL, possibly indicating the need for palliative care involvement, are objectives of this study. To inform data collection and analytical strategies of the main study, the following three areas were systematically reviewed prior to commencing and planning primary data collection: (1) symptom prevalence and prevalence of QOL-related problems, (2) longitudinal changes in symptom prevalence and QOL in existing research studies, and (3) independently associated factors of QOL. Two of these were published as meta-analyses in journals and these publications are reprinted in the following chapters.

2.2.2.1 Prevalence of symptoms in patients with multiple myeloma – a systematic review and meta-analysis

Article published in the *European Journal of Haematology* (369)

Authors: Christina Ramsenthaler, Pauline M. Kane, Wei Gao, Richard J Siegert, Polly M. Edmonds, Steve A. Schey, Irene J. Higginson

Title: Prevalence of symptoms in patients with multiple myeloma: A systematic review and meta-analysis

Running head: Symptom prevalence in multiple myeloma

Article type: Systematic review and meta-analysis

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Abstract

Objectives. Multiple myeloma (MM) is an incurable haematological disease. Due to novel agents, overall survival has improved in this group, yet there are no systematic reviews to understand the symptom profiles resulting from disease and treatment-related toxicities. We aimed to synthesise data on prevalence of symptoms in patients with MM.

Methods. A systematic database and grey literature search was conducted in 6 databases. Random effects meta-analysis with inverse variance weighting to pool prevalence data was performed.

Results. 36 studies were included of which 34 studies (N = 3,023) provided data for meta-analysis. 27 distinct symptoms were reported, with the majority of studies focusing on pain (n=27), fatigue (n=19) and problems with functioning (n=15). The most prevalent symptoms were fatigue (98.8%, 95% CI 98.1 – 99.2%), pain (73%, 39.9 – 91.7), constipation (65.2%, 22.9-92.2) and tingling in the hands/feet with 53.4% (0.4-99.7). The most common problems were decreased physical functioning (98.9%, 98.2 – 99.3), decreased cognitive functioning (80.2%, 40 – 96.1) and financial difficulties (78.4%, 39.1 – 95.4). These problems were present in newly diagnosed to advanced disease stage.

Conclusions. Optimal quality of life and good symptom management in this incurable disease can only be achieved by routinely assessing symptoms throughout the disease trajectory.

Key words: Multiple myeloma, symptom burden, signs and symptoms, systematic review, prevalence

Introduction

Multiple myeloma is the second most common haematological cancer in the UK with an annual incidence of 6.9 cases per 100,000 population (1). Cancer registries estimate that there are 4,040 new cases each year in the UK and 41,719 new cases in Europe (2). The incidence has increased in recent years, due to advances in treatment and overall ageing of the society (3). Despite these improvements, multiple myeloma remains an incurable disease and patients will eventually die from it or the consequences of its treatment. Estimates for the year 2016 range from 2,799 deaths in the UK to 20,462 in Europe (2).

The introduction of novel agents such as bortezomib and, lately, lenalidomide and pomalidomide (4, 5), and the wide-spread use of high-dose melphalan with autologous stem cell transplantation (ASCT) as first-line treatment means that now more patients with multiple myeloma live with their illness for longer than in the past (4, 6). These new treatment agents have also resulted in a varied profile of adverse events and long-term treatment-related toxicities, among them most prominently treatment-induced peripheral neuropathy (7, 8). Moreover, with multiple myeloma being a cancer primarily of older age, with a median age at diagnosis of 73 to 75 (9), co-morbid chronic and progressive diseases among all myeloma patients will also become more common. These trends bring with it that health care needs and the need for managing the various disease- and treatment-related problems become much more complex.

Despite the extensive study of symptom burden in solid tumours, particularly in the advanced stages of disease (10–13), there has been little reliable and valid observational evidence on symptom burden in haematological diseases. To date, no systematic review focusing on haematological cancer populations has been published. A few non-systematic reviews describe burden in stem cell transplantation (SCT) samples, but mainly in form of quality of life with pooling of symptom prevalence a secondary objectives at best (14–16). This may be because only few prospective studies have documented the prevalence of symptoms in patients with haematological disease. A few notable exceptions employ a population perspective. These studies have reported a mean of 8.8 symptoms (17, 18), an average that is lower than that of 11 symptoms reported for advanced cancer (10) but sufficiently high to indicate substantial need for effective symptom management in this group.

In this systematic review, rather than including all haematological cancers we focus on the symptom prevalence reported in multiple myeloma. Due to its more chronic nature and the cumulative toxicities that patients experience from multiple lines of treatment, the symptom burden can be profound (e.g. bone pain, fatigue, gastrointestinal symptoms, peripheral neuropathy) (19). Multiple myeloma can thus be exemplary for haematological cancers with a longer disease trajectory. Also, a number of symptom

and outcome measurement tools have been developed for multiple myeloma, which makes the study of symptom prevalence more valid and reliable (20, 21).

The aim of this systematic review is to synthesise the data on the point prevalence of symptoms and side effects as well as other health-related quality of life (HRQOL) problems and concerns in patients with multiple myeloma.

Materials and methods

Literature search and data extraction

This systematic review and meta-analysis follows the recommendations from the PRISMA statement (22). We searched the following databases on 26th May 2016, to identify studies reporting symptom prevalence in multiple myeloma: Medline (from 1950), Embase (from 1980), PsycINFO (from 1806) (all via Ovid), CINAHL (from 1981, via Ebscohost), and the Web of Science (from 1900, via Thomson Reuters). The search strategy used a combination of medical subject headings (MeSH, exploded) and key words, adapted to individual databases, to search for the following concepts: "symptoms" AND "multiple myeloma" AND "prevalence". The search strategy can be found in the Appendix. To account for database limitations, the search was supplemented by (a) identification of reports and grey literature in GoogleScholar, (b) search for conference abstracts in Web of Science, (c) a hand search of six relevant journals. Finally, we further searched the reference lists of all included studies and used citation tracking searches in Scopus (via Elsevier).

Articles written in English, French, German, Italian and Spanish were considered for inclusion. Study inclusion criteria were: a) reporting data on symptoms and other problems using a validated or piloted self-report instrument for establishing symptom prevalence; b) for an adequate representation at least >30% of myeloma participants in the sample, including mixed haematological, cancer or palliative samples (Studies were also included if prevalence data was reported separately for the subgroup of myeloma patients in a study in which the overall proportion of multiple myeloma patients was less than 30%); c) original research of a quantitative design, including descriptive and analytical observational studies, quasi-experimental and experimental studies and secondary analyses of randomised controlled trials. Studies were excluded if they reported their findings in a language not included in the list above. Further exclusion criteria were studies using a case report/series design, systematic reviews and qualitative designs.

One reviewer assessed titles, abstracts and full-texts. 30% of full-texts were assessed independently by a second reviewer. Data extraction using a standardised form and recording aims and characteristics of the study, the study population and its clinical characteristics (e.g. stage of disease, treatment history) was completed by one reviewer. Disagreement at any stage was resolved in discussion with the senior

investigator (I.J.H.). Methodological quality was assessed using two checklists, one for appraising the methodological quality of randomised controlled trials (23), and one assessing cohort studies and descriptive observational studies (24). Studies were checked for the likelihood of selection bias, confounding, study design, blinding and randomisation (for clinical trials), data collection methods, statistical analysis and reporting of withdrawals. Based on these criteria, studies were scored as weak, moderate or strong evidence (23, 25). Quality was assessed independently by a second reviewer. Any disagreement between reviewers was solved by consensus.

Analytical methods and meta-analysis

Prevalence figures were combined separately per symptom using meta-analysis, if comparability of study and patient characteristics in included studies permitted synthesis. Data were pooled using a random-effects model since some studies included samples not solely consisting of myeloma patients. Mixed samples represent a source of heterogeneity, making the estimation of several population point prevalence rates likely (26). Raw prevalence figures from included studies were logit transformed and synthesised using the inverse variance method. The final pooled logit was back transformed using the exponential function, resulting in pooled prevalence and 95% confidence intervals (27). For each symptom, if possible, two prevalence estimates were derived, one for mild to moderate symptom severity and one for severe symptom severity. For the quality of life subscales from the EORTC QLQ-C30 questionnaire, the prevalence of a problem indicated on the respective subscale was determined using a cut-off of less than 66 for a mild problem and less than 34 as a severe problem (18). Heterogeneity was estimated using Cochran's *Q*-statistic (28) at a significance level of 0.10. From this statistic, the I^2-statistic was calculated with an acceptable level of heterogeneity being defined as I^2 equalling less than 70% (29, 30). We anticipated the following sources of heterogeneity: clinical diversity, stemming from inclusion of mixed samples and populations, methodological heterogeneity and heterogeneity from using different symptom assessment tools and classification systems. Subgroup analysis of disease stage and treatment group was planned, depending on presence of at least three studies per subgroup. Meta-analysis was performed using the *metafor* package (31) in the statistical programme *R* (32).

Results

The electronic database searches yielded 16,236 records. An additional 5 records were added after hand searches and grey literature searches. Thirty-six studies were included in the systematic review, with 34 studies contributing data to meta-analysis. Reasons for exclusion are shown in Figure 1.

[Insert Figure 1]

Clinical and methodological characteristics of included studies

The characteristics of included studies are presented in Table 1. The majority of studies used cross-sectional designs (n = 19). Four randomised clinical trials and four quasi-experimental studies were included. Almost an equal proportion of studies focused on SCT populations (n = 16) or chemotherapy/outpatient populations (n = 15). Three studies investigated new chemotherapeutic agents in an RCT. The setting was not reported in two studies. Of the 36 included studies only nine used determining symptom prevalence as the explicit aim. By far the most common HRQOL tool was the EORTC-QLQ-C30 used in 16 studies, either solely or in conjunction with its myeloma module (MY-20). Validated symptom assessment tools were the MDASI-BMT (n = 2) and the MDASI-MM (n = 2). Some studies used other HRQOL tools, such as the SF-36, SF-12 or measures from the FACT-group. Some studies used single symptom measures like the Brief Pain Inventory or specific mental health assessments. Four studies used tools that had a purpose other than symptom assessment and five studies used no validated tools to ascertain symptom prevalence. The proportion of myeloma patients in included studies varied from as little as 4.8% (33) (those were studies that reported data separately on the myeloma subgroup and could therefore be included in the meta-analysis) to 100% in almost three quarter of the included studies (n = 25). Fifteen studies did not report the stage of disease. The remaining studies consisted of newly diagnosed patients (n = 9), with 12 studies including a proportion of advanced stages.

[Insert Table 1]

Methodological quality

Twelve of the included studies obtained a low methodological quality score (see Table 1), 17 were of medium and seven were of high quality. The seven high-quality studies comprised the randomised controlled trials and those epidemiological observational studies with a focus on establishing symptom prevalence. Bias was introduced in original studies due to attrition in longitudinal designs, with little information on those participants lost to follow-up, and scant reporting of the recruitment process and clinical characteristics. Further problems were the absence of clear hypotheses and poor statistical analysis.

Symptom prevalence

27 symptoms were identified across the 35 studies (see Table 2). The four most prevalent symptoms, occurring in at least 50% of study participants, were fatigue, with a pooled prevalence of 98.8% (95% CI 98.1 – 99.2), constipation (66.5%, 23.5 – 92.8), pain (58.6%, 8.8 – 95.2), and tingling in the hands/feet (53.4%, 0.4 – 99.7). Fatigue, pain and constipation were also the three symptoms that, in samples of myeloma patients that were severely affected by these symptoms, reached pooled prevalence rates of >40% (59.7% severe fatigue, 45.2% severe constipation, and 44.7% severe pain). Psychological symptoms in form of distress, anxiety and depression were present with a pooled

prevalence of 22.3% for depression (95% CI 0.3 – 96.2) to 35.7% (1.0 – 96.9) for anxiety. If only clinically relevant cases of anxiety and depression were considered, based on cut-off criteria, a pooled prevalence of 26.7% for anxiety and of 23.6% for depression was found. Pain, fatigue, sleep problems and depression were the symptoms the most frequently examined in included studies.

[Insert Table 2]

Prevalence of quality of life problems

Decreased physical functioning, in the original studies determined by values of <66.7 on the EORTC subscale (18), was the most common HRQOL problem with a pooled prevalence of 98.9% (95% CI 98.2 – 99.3%), followed by decreased cognitive functioning (80.2%, 40.0-96.1%), and financial difficulties with a pooled prevalence of 78.4% (39.1 – 95.4%). Decreased role, emotional and social functioning also had prevalence rates of >50%. Severely decreased role functioning and severe financial difficulties were problems with a pooled prevalence of 46.7% and 43.3%, respectively. The three subscales with the lowest pooled prevalence rates were severe disease symptoms, severe worry about dying or the future and severely decreased cognitive functioning. However, worry about dying/future and cognitive functioning both had higher prevalence rates when being of mild to moderate severity.

Discussion

27 distinct symptoms were reported in the 36 included studies of this meta-analysis of symptom prevalence in multiple myeloma. Most studies focused on pain (75%), fatigue (53.1%), and aspects of functioning (40.6%). Gastrointestinal symptoms, cognitive symptoms and psychological symptoms were assessed in a quarter to a third of studies. The most common symptoms were fatigue, pain, constipation, and peripheral neuropathy, present from 53.4% of patients to almost 100%. Further bothersome symptoms came from the psychological domain, as well as breathlessness and sleep problems. A pooled prevalence of nearly 25% was found for sexual dysfunction. Myeloma patients demonstrated severely decreased functioning in several domains, predominantly role and social functioning. Almost half of patients expressed worry about dying and the future and nearly 80% reported financial difficulties of which 43.3% were severe.

These findings indicate that there is a large number of symptoms that occur frequently in high numbers of patients. These figures are comparable to symptom reviews in the general cancer population (12) and in advanced cancer patients, in which studies reported 11 to 56 distinct symptoms with the most prevalent symptoms being fatigue, lack of energy, pain, sleep problems and breathlessness (10–12, 65). Some of these reviews also investigated symptom severity, an analysis only indirectly achieved in this meta-analysis through the separate pooling of mild to moderate symptoms versus severe symptoms.

It remains challenging to analyse symptom prevalence over time in multiple myeloma. Some of the reported symptoms can have disease-related or treatment-related aetiologies. Only few studies presented longitudinal information on prevalence and inadequate power precluded meta-regression of variables such as treatment history and disease characteristics. However, analysing some of the symptoms that could be related to treatment toxicities and hence later stages of disease showed that not all of these confirm to this pattern. While neurotoxicity is reported in studies with mainly advanced patients in later stages of myeloma (19, 47, 51, 52), fatigue, sexual problems, and financial difficulties are present at all stages. Sexual problems in particular were also reported by patients with newly diagnosed disease pre-transplantation (58). The same was observed for financial difficulties, present in newly diagnosed samples, samples with mixed disease stages and studies reporting baseline evaluation of SCT patients (18, 42, 47, 48, 50,53, 54). A high prevalence of fatigue was also reported in these studies (17, 38, 60).

This meta-analysis was a cross-sectional analysis of symptom prevalence. The longitudinal studies in this review all included mixed samples of SCT patients. In these studies, a general pattern of worsening of symptoms and functioning variables over the course of the transplantation process is reported, to either nadir (17) or to a point 2-3 months post transplantation (37, 39, 54), with the notable exception of depression and anxiety which were reported to not return to baseline levels and even rise after transplantation in one study (60). Nonetheless, the derivation of a general course of symptom prevalence is hampered by different assessments used in pre-, peri- and post-transplantation periods. What this data shows, however, is the high prevalence of problems and symptoms and the general burden that myeloma patients experience even at baseline and in the time period leading to transplantation.

Methodological limitations

Aggregating data on symptom prevalence in multiple myeloma was hampered by a number of methodological factors. The wide confidence intervals that were observed in the meta-analysis, in some cases spanning 99%, indicate high heterogeneity. First, this stems from the definition of each symptom depending on the method of assessment. Some studies used multi-item screening questionnaires with clinical cut-off criteria while others utilised single items. Second, studies differed in their design, the type of prevalence they assessed and sometimes even the numerator (number of events versus number of patients). Also, studies had different length of follow-up. Since comparability was not given, this data and the longitudinal change in symptom prevalence was not included in the meta-analysis. Third, patients at different stages of the disease were included, with stage often not reported. This might well affect the prevalence estimates for specific symptoms, in particular peripheral neuropathy and fatigue. As illness progresses, new symptoms emerge as side-effects of treatment. Fourth, some studies used non-validated measurement tools to ascertain symptom burden, some based on recorded data. Moreover, a symptom was sometimes counted only when exceeding a

predefined severity level. We did not mix these two groups in the meta-analysis. However, these factors could likely lead to systematic underreporting of symptoms. Lastly, the inclusion of mixed samples of haematological cancer could have distorted the symptom profile. Since we used tight inclusion criteria for the type of study and a language restriction, publication bias may have occurred. Although meta-analysis can improve the power of analysis by pooling results from small studies, some symptoms were reported in a small number only which diminishes the validity of the pooled estimates.

Clinical implications

Multiple myeloma is an example of an incurable haematological cancer in which, due to improvements in therapy, patients now live a comparably long time of 5-10 years (Kumar *et al*, 2008) with their disease. New developments warrant insights into long-term toxicities and better patient management and care, especially towards the end of life (66). In 1996, a position statement was issued to advocate good symptom management, improving functioning and HRQOL alongside survival as the goal of effective cancer treatment (67). This also reflects patients' experiences, who commonly cite QOL as one of their primary concerns, both at initial diagnosis as well as during later stages (68–70). Moreover, HRQOL has been shown to correlate with survival both in newly diagnosed (44, 64, 71) and in relapsed, refractory patients (72). Thus, symptoms provide meaningful information (73) and HRQOL yields prognostic information in conjunction with clinical markers (74). The challenge is the routine integration of collecting PRO information in the clinical setting. Routine collection of PROs has been shown to be feasible and efficient in SCT (75), approaches that could be translated to the myeloma setting.

Conclusion

This meta-analysis identified pain, fatigue and aspects of functioning as most common and burdensome symptoms in multiple myeloma. Some problems such as financial difficulties and sexual concerns, traditionally associated with later stages of disease, were present with a high prevalence even shortly after diagnosis or at the beginning of SCT. Awareness and studies of the symptom patterns over time may help optimise symptom management for patients with multiple myeloma.

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Conflict of interest and sources of funding

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The corresponding author had full access to all the data and had responsibility for the decision to submit for publication. The views expressed in this publication are those of the author(s) and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health.

Supporting information

Additional supporting information may be found in the online version of the article:

Figure S1. MeSH (Medical Subject Headings) terms and key words used in the systematic literature search.

Figure S2. Forest plot of the most common symptoms and problems in multiple myeloma with a pooled prevalence estimate of >50%.

Table S1. Change in symptom prevalence and quality of life over time in included longitudinal studies

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Table I. Clinical and methodological characteristics of the included studies

Study, sample size (% MM)	Study Design	Aim	Patient characteristics, treatment and stage	Measurement instrument	Quality score
Anderson *et al*, 2007 (17) N = 100 (60)	Longitudinal observational study	Assessing severity of symptoms during acute phase of autologous SCT and over time	Mean age 53.6 (SD 9.7), 60% men Melphalan conditioning and ASCT	MDASI-BMT	++
Bergerot *et al*, 2015 (33) N = 104 (4.8)*	Longitudinal observational study	Exploring the impact of gender and grade of cancer on distress, anxiety and depression in patients on chemotherapy	Mean age 52.1 (SD 19.9), 49% men Mixed haematological cancer patients starting chemotherapy, newly diagnosed, 66.3% high grade	Distress Ther. HADS	++
Bohsain, 2014 (34) N = 24 (100)	Quasi-experimental study	Determining the HRQOL of patients treated with vertebroplasty	Mean age: 60 (SD 12), 45,8% men Vertebroplasty vs conservative treatment	VAS 0-10 for pain	+
Boland *et al*, 2014 (35) N = 32 (100)	Cross-sectional study	To characterise the holistic needs of advanced but stable MM patients	Mean age 60 (range 41-71), 53.1% men Mean lines of treatment: 3 (range 2-6), having undergone at least one HSCT and subsequent line	Holistic needs assessment instrument SPARC	+
Booker *et al*, 2009 (36) N = 56 (100)	Cross-sectional study	Investigating the relationships among physiologic variables, fatigue and quality of life in MM	Mean age 62 (SD 10.8), 54% men Treatment: NR Stage: 23% ISS stage I, 21% ISS stage II, 50% ISS stage III	EORTC QLQ-C30 FACT-F	++
Campbell *et al*, 2011† (37) N = 173 (31.2)	Longitudinal observational study	Monitoring HRQOL and psychological functioning 12 months post ASCT	Mean age 53 (SD 14), 65% men Melphalan conditioning and ASCT	CES-D Distress Ther. SF-36	++
Coleman *et al*, 2002 (38) N = 87 (100)	Quasi-experimental study	Comparison of symptoms in outpatient ASCT with those that required unplanned hospital admission	Mean age 51 (SD 8.1), 70% men ASCT	Clinical database	+
Coleman *et al*, 2011 (39) N = 187 (100)	Randomised clinical trial	Describing fatigue, sleep, pain, mood, and performance status and the relationships among these variables	Mean age 56 (SD 10) Exercise intervention for tandem SCT Stage: Newly diagnosed MM	FACT-G FACT-F, FACT-Pain POMS	++
Delforge *et al*, 2015 (40) N = 1623 (100)	Randomised clinical trial	Comparison of HRQOL in patients with newly diagnosed multiple myeloma in the treatment arms of the FIRST trial	Median age 73 (range 40-92), 52.6% men Lenalidomide plus low-dose dexamethasone versus MPT Stage: Newly diagnosed	EORTC QLQ-C30 EORTC QLQ-MY20	+++
Dimopoulos *et al*, 2014 (41) N = 459 (100)	Randomised clinical trial	Sub-analysis of the impact of individual predictive factors on HRQOL	Median age 71, 49.7% men MPR plus lenalidomide maintenance, MPR, MP Stage: Newly diagnosed	EORTC QLQ-C30	+++
Espinoza-Zamora *et al*, 2015 (42) N = 98 (100)	Cross-sectional study	Validation of the EORTC QLQ-MY 20 in Mexico	Mean age: 58.1 (SD 11.2), 60.6% men Outpatient MM patients at university hospital	EORTC QLQ-C30, EORTC QLQ-MY20	++
Federico *et al*, 2013† (43)	Cross-sectional study	Evaluation of a multidisciplinary palliative care team on HRQOL and	Mean age: NR, % men NR 40 patients 1st line treatment, 5 with relapsed disease	MDASI-BMT	+

N = 60 (100)		symptom assessment	Stage: 15 patients with advanced stage		
Gulbrandsen *et al*, 2001 (44) N = 334 (100)	Non-randomised clinical trial	Exploring the impact of high-dose therapy with ASCT on HRQOL followed by interferon maintenance	Median age 54, 36.8% men 221 patients receiving intensive therapy, newly diagnosed, Stage: 13 stage I, 108 stage II, 213 stage III	EORTC QLQ-C30	++
Jacobs *et al*, 2007 (45) N = 101 (63)	Longitudinal observational study	Validition of the FACT-Cog in patients having completed allogeneic or autologous HSCT	Mean age: 52.7 (SD 12.2) % male: 56.4%	FACT-Cog EORTC QLQ-C30	++
Johnsen *et al*, 2009 (18) N = 470 (11)*	Cross-sectional study	Investigating the prevalence of symptoms and problems in a representative sample of patients	Mean age: 63, 53% male Mean 2-5 years post diagnosis, 22% on treatment 95% outpatients	EORTC QLQ-C30	+++
Jones *et al*, 2013a (46) N = 48 (100)	Longitudinal observational study	Evaluation cognitive functioning one and three months post HSCT	No demographic or clinical data Post induction therapy for HSCT	MDASI-MM Cognitive test battery	+
Jones *et al*, 2013b (21) N = 132 (100)	Longitudinal observational study	Validation of the MDASI-MM in multiple myeloma	Mean age: 62.5 (SD 10), 64.3% men Induction chemotherapy or undergoing ASCT Newly diagnosed	MDASI-MM	+
Jordan *et al*, 2013 (19) N = 154 (100)	Cross-sectional study	European multicentre study to quantify symptom level and treatment-related side effects of novel agents	Mean age: 66.4 (SD 10), 63% men Mean 3.7 years post-diagnosis, 52% on treatment	EORTC QLQ-C30, EORTC QLQ-MY20	+++
Kiley *et al*, 2016 (47) N = 41 (100)	Cross-sectional study	Determining symptom prevalence and HRQOL and comparison to general and cancer population	Mean age: 63.7 (SD 11.2), 59% men Haematology day unit in tertiary referral centre, 30% have received stem cell transplant and all patients on disease-modifying treatment	QLQ-C30 QLQ-MY20 HADS	++
Kontodimopoulos *et al*, 2012 (48) N = 89 (100)	Cross-sectional study	Validation study of the Greek version of the EORTC QLQ-C30 and QLQ-MY20	Mean age: 64.2 8SD 11.3), 56.2% male Outpatient MM, mean duration 3.9 years, 46.1% previous HSCT 41.6% ISS stage I, 32.6% ISS stage II, 19.1% ISS stage III	EORTC QLQ-C30, EORTC QLQ-MY20	++
Lamers *et al*, 2013 (49) N = 114 (100)	Cross-sectional study	Examining interest in psychosocial interventions at time of diagnosis and associated factors	Mean age: 62 (SD 10.2), 51.8% men Outpatient myeloma clinic at time of diagnosis Newly diagnosed	PHQ-9 GAD -7	+
McQuellon *et al*, 2010† (50) N = 55 (34.5)	Cross-sectional study	Three-months post HSCT data reported on quality of survivorship, originally longitudinal observational study	Mean age: 58 (SD 13.8), 72% men Patients post ASCT	Surveillance questionnaire FACIT-Satisfaction	++
Molassiotis *et al*, 2011 (51) N = 132 (100)	Cross-sectional study	To identify the nature and range of needs, as well as levels of HRQOL, of both patients with MM and their partners	Mean age: 62 (SD 8.8), 61.4% men Patients from specialist transplant centres, district hospitals, mean 2.8 years post diagnosis and 68.1% prior ASCT	Cancer Survivors' Unmet Needs, EORTC QLQ-C30, EORTC QLQ-MY20	++
Mols *et al*, 2012 (52) N = 154 (100)	Longitudinal observational study	Describing HRQOL and disease-specific complaints of patients with MM up to 10 years post diagnosis	Median age 66, 54.8% men Survey from cancer registry, 0 – 4 years post diagnosis, various treatments	EORTC QLQ-C30 EORTC QLQ-MY20	+++
Pamuk *et al*, 2012† (53)	Cross-sectional study	Determining prevalence of symptoms and problems and predictors for HRQOL	Mean age: 62.4 (SD 10.1), 61% men Tertiary referral centre, treatment NR	EORTC QLQ-C30	+

N = 332 (27.9)					
Pillay *et al*, 2015 (54) N = 60 (42)	Longitudinal observational study	Examining the impact of sense of coherence on anxiety, depression and HRQOL	Mean age: 51.1 (SD 12.5) Patients undergoing allogeneic or autologous SCT, mean 2.1 years post diagnosis	BSI-18 FACT-BMT	++
Poulos *et al*, 2001 (55) N = 206 (100)	Cross-sectional study	Determining levels of pain intensity and pain interference in patients with MM, and the relationship to HRQOL	Mean age: 62.9 (SD 10.3), 67% men Clinical database with patients treated at hospital Mean 3 years since diagnosis, 11% previous HSCT	BPI Quality of Life Scale POMS	++
Priscilla *et al*, 2011 (56) N = 105 (5.7)*	Cross-sectional study	Determining the prevalence of symptoms and problems in hospitalized haematological cancer patients	Mean age 40.4, 47.6% men Haematological ward in one hospital, treatment history NR	EORTC QLQ-C30	+
Sborov *et al*, 2015 (57) N = 16 (100)	Phase 1 trial	Evaluation of combination of Vorinostat and lenalidomide maintenance post ASCT	Mean age: 58 (range 41-67), 62.5 % men Vorinostat and lenalidomide maintenance after ASCT Median ISS stage 2	CES-D BFI and BPI FACT-G	+
Sherman *et al*, 2003 (58) N = 61 (61)	Cross-sectional study	Determining the feasibility of early systematic screening and evaluating levels of symptomatology	Mean age: 57 (SD 12.3), 64% men Patients undergoing baseline evaluation for conditioning and ASCT	SF-12, POMS-F, BPI HADS, FACIT-sexual concerns	++
Sherman *et al*, 2004 (59) N = 213 (100)	Cross-sectional study	Examining psychosocial and functional deficits among MM patients at their initial diagnostic evaluation	Median age: 59 (range 31-81), 60% men Patients undergoing baseline evaluation for conditioning and ASCT	SF-12	+++
Sherman *et al*, 2009 (60) N = 94 (100)	Longitudinal observational study	Determining HRQOL and psychosocial adjustment and medical and demographic correlates	Mean age: 55.7 (SD 9.2), 61.7% men Autologous SCT, median 6 months post-diagnosis Stage: 18.1% stage I, 5.3% stage II, 71.3% stage III	FACT-BMT Satisfaction with Life BSI	+++
Sloot *et al*, 2015 (61) N = 21 (100)	Cross-sectional study	Determining the impact of analgesics and their side effects on HRQOL	Mean age 65 (SD 9), 47.6% men Patients using pain medication at tertiary centre, mean time since diagnosis 3.3 years	EORTC QLQ-C30	++
Slovacek *et al*, 2007 (62) N = 56 (57)	Cross-sectional study	Analysing the effect of selected psychosocial aspects on HRQOL in patients with MM and lymphoma	Mean age 60, 53.6% men Patients undergoing ASCT at tertiary centre	EQ5D	+
Vera-Llonch *et al*, 2007 (63) N = 115 (100)	Retrospective cross-sectional study	To assess the relationship between oral mucositis and adverse clinical and economic outcomes of ASCT in MM	Mean age 54.4 (SD 8.8), 58.3% men Patients undergoing high-dose melphalan conditioning and ASCT	Chart review	+
Wisløff *et al*, 1996 (64) N = 524 (100)	Randomised clinical trial	Determining the effect of interferon on HRQOL	Median age 67, 64.8% men Patients receiving melphalan and prednisone plus interferon-alpha versus melphalan-prednisone Stage: 10.5% stage I, 38.9% stage II, 61.8% stage III	EORTC QLQ-C30, Additional 11 items to report common interferon toxicities	++

ASCT, autologous stem cell transplantation; BFI, Brief Fatigue Inventory; BPI, Brief Pain Inventory; BSI-18, Brief Symptom Inventory 18-item Scale; CES-D, Center for Epidemiological Studies Depression Scale; Distress Ther., Distress Thermometer; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer quality of life questionnaire C30; EORTC QLQ-MY20, European Organization for Research and Treatment of Cancer quality of life questionnaire: Myeloma module; EQ5D, EuroQOL group health status 5D questionnaire; FACIT, Functional Assessment of Chronic Illness Therapy; FACT-BMT, Functional Assessment of Cancer Therapy Bone Marrow Transplantation Scale; FACT-Cog, Functional Assessment of Cancer Therapy Cognitive Scale; FACT-F, Functional Assessment of Cancer Therapy Fatigue scale; FACT-G, Functional Assessment of Cancer Therapy General scale; FACT-Pain, Functional Assessment of Cancer Therapy Pain scale; GAD-7, Generalized Anxiety Disorder 7-item Scale; HADS, Hospital Anxiety and Depression Scale; HRQOL, health-related quality of life; HSCT, hematopoietic stem cell transplantation; ISS, International Staging System;

MDASI-BMT, M. D. Anderson Symptom Inventory – bone marrow transplantation module; MDASI-MM, M. D. Anderson Symptom Inventory – myeloma module; MM, mulitple myeloma; MP, Melphalan and prednisone; MPR, Melphalan, prednisone and lenalidomide; MPT, Melphalan, prednisone and thalidomide; N, sample size; NR, not reported; PHQ-9, Patient Health Questionnaire 9-item Depression Scale; POMS: Profile of Mood States; SCT, stem cell transplantation; SD, standard deviation; SF-12, Medical Outcome Study 12-item Short Form Health Survey; SF-36, Medical Outcome Study 36-item Short Form Health Survey; SPARC, Sheffield Profile for Assessment and Referral for Care questionnaire; VAS, visual analogue scale

*Quality score: For observational studies following De Jonge *et al*'s () scoring algorithm with low (<45 points), medium (≥45 to <60), and high quality (≥60). For (quasi-) experimental studies following Thomas *et al*'s () scoring algorithm with a rating of weak, moderate or strong assigned to each of the six domains and a global rating of strong given if at least four strong ratings and no weak ratings existed; a rating of moderate given to studies with less than four strong ratings and one weak rating; and a weak rating given to studies with two or more weak ratings in domain scores.

†Abstract only.

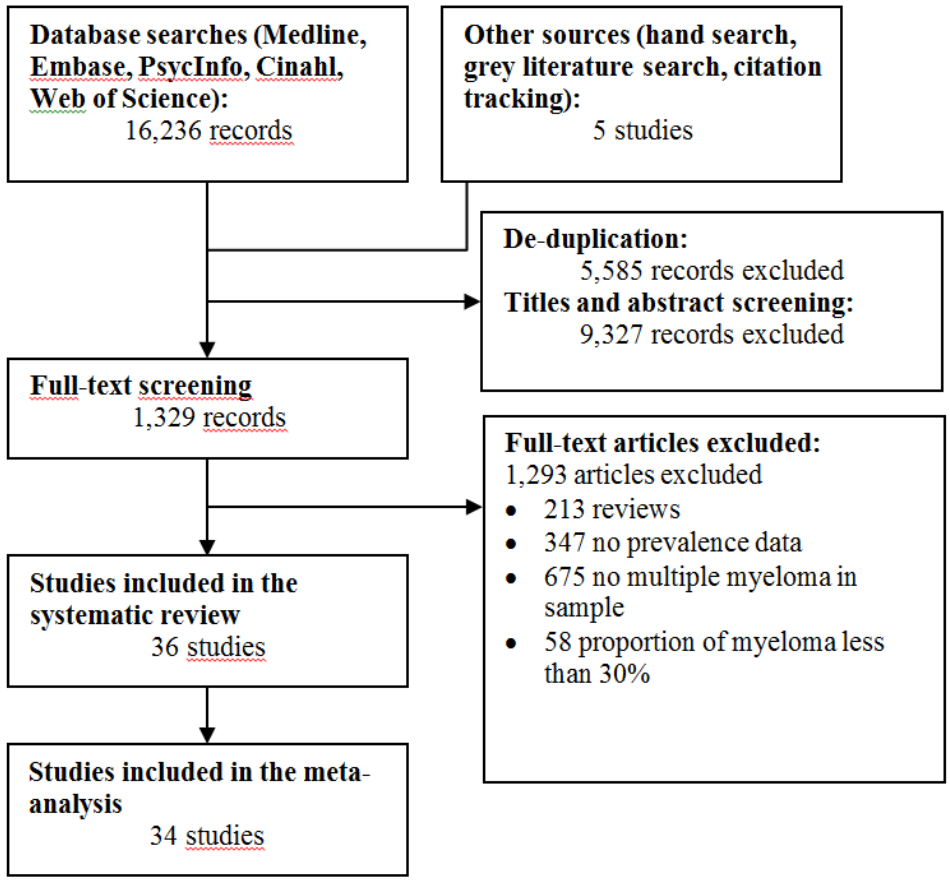
Table II. Prevalence of symptoms and quality of life problems

Symptom	Number of studies	Number of subjects	Pooled prevalence (%)	95% CI	I^2 (%)
Pain	15	1882	58.6	8.8 – 95.2	12.0
Severe pain	10	1136	44.7	2.2 – 96.7	24.7
Bone aches	4	572	41.0	0 - 1	100.0
Fatigue	13	1204	98.8	98.1 – 99.2	0.2
Severe fatigue	7	620	59.7	12.9 – 93.7	11.2
Weakness	3	264	21.6	0.1 – 99.7	100.0
Tiredness	3	318	46.9	0.2 – 99.7	100.0
Sleep problems	11	1075	34.5	3.8 – 87.4	100.0
Severe sleep problems	4	245	32.1	1.9 – 92.1	36.6
Feeling sick	2	254	13.5	0.0 – 100.0	37.9
Dizziness	3	428	36.8	0.2 – 99.5	100
Drowsiness	3	308	40.6	0.3 – 99.4	9.8
Appetite loss	8	770	42.7	5.3 – 90.8	23.4
Severe appetite loss	4	245	32.8	2.0 – 92.2	26.6
Nausea	4	541	16.9	0.1 – 99.0	50.7
Vomiting	2	109	9.5	0.1 – 99.4	12.0
Nausea/vomiting	10	981	17.7	1.1 – 80.5	21.4
Severe nausea/vomiting	4	245	2.7	0.1 – 59.7	2.2
Diarrhoea	8	805	40.7	4.8 – 90.4	6.8
Severe diarrhoea	4	245	21.1	0.8 – 89.9	5.7
Constipation	7	639	66.5	23.5 – 92.8	13.2
Severe constipation	4	245	45.2	4.6 – 93.4	17.9
Breathlessness	7	540	36.6	3.3 – 90.7	36.3
Severe breathlessness	4	245	33.0	1.8 – 92.2	17.0
Cough*	1	253	42.0	23.9 – 60.0	-
Mouth problems	7	1047	21.4	0.1 – 98.3	43.6
Severe mouth problems*	1	154	17.1	1.4 – 35.6	-
Problems remembering	3	281	42.6	0.1 – 99.9	100.0
Difficulty paying attention*	1	100	8.0	1.3 – 29.1	-
Tingling in hands/feet	4	481	53.4	0.4 – 99.7	98.3
Severe tingling*	1	154	32.0	10.8 – 53.1	-
Distress	4	379	27.8	0.0 – 100.0	100
Anxiety	10	835	35.7	1.0 – 96.9	46.1
Case of anxiety	8	720	26.7	0.2 – 98.4	100
Depression	11	1028	22.3	0.3 – 96.2	86.4
Case of depression	9	774	23.6	0.3 – 97.3	73.5
Sexual problems	3	115	23.5	0.2 – 98.1	51.5
Muscle cramps	2	176	6.9	0.0 – 99.5	21
Peripheral edema	2	176	6.5	0.0 – 99.5	29
Quality of life problems					
Decreased physical functioning	13	1424	98.9	98.2 – 99.3	0.5
Severely decreased physical functioning	4	245	27.3	1.4 – 91.1	12.5
Decreased role functioning	9	941	67.0	21.2 – 93.9	17.3
Severely decreased role functioning	4	245	46.7	5.0 – 93.6	28.4
Decreased emotional functioning	9	1005	57.7	12.5 – 92.9	10.4
Severely decreased emotional functioning	4	245	26.3	1.3 – 90.8	10.5

Decreased cognitive functioning	5	577	80.2	40.0 – 96.1	3.3
Severely decreased cognitive functioning	4	245	14.1	0.4 – 87.2	20.3
Decreased social functioning	8	855	58.0	12.2 – 93.2	6.8
Severely decreased social functioning	4	245	28.6	1.5 – 91.5	23.5
Most severe disease symptoms	2	187	1.5	0.0 – 100.0	100
Most severe side effects	3	219	15.1	0.0 – 99.5	7.4
Worry about dying/future	6	569	49.7	1.1 – 98.9	16.4
Severe worry about dying	3	341	11.9	0.0 – 100.0	43.6
Problems with body image	3	228	41.3	0.1 – 99.7	13.5
Financial difficulties	7	673	78.4	39.1 – 95.4	5.0
Severe financial difficulties	4	245	43.3	4.2 – 93.1	6.9

*No pooled prevalence (only one study).

Fig 1. Flow chart of literature search results and study selection



SUPPLEMENTAL MATERIALS

Prevalence of symptoms in patients with multiple myeloma: A systematic review and meta-analysis

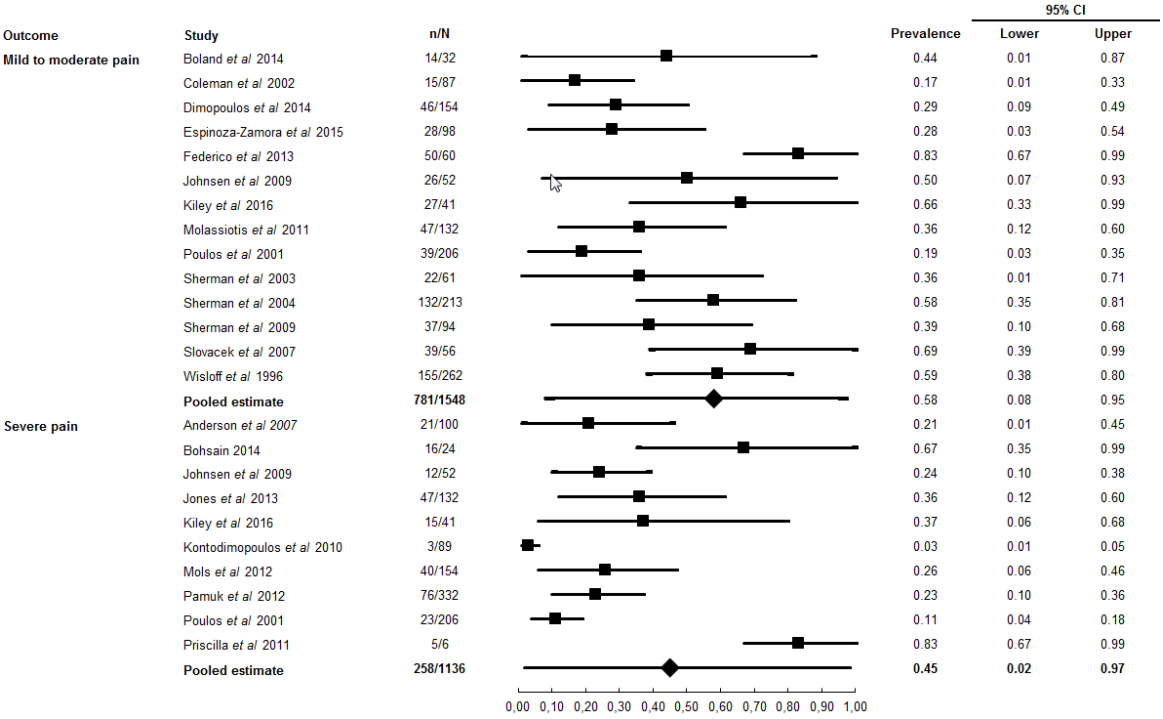
Christina Ramsenthaler, Pauline Kane, Wei Gao, Richard J. Siegert, Polly M. Edmonds, Stephen A. Schey, Irene J. Higginson

Table S1. MeSH (Medical Subject Headings) terms and key words used in the systematic literature search.

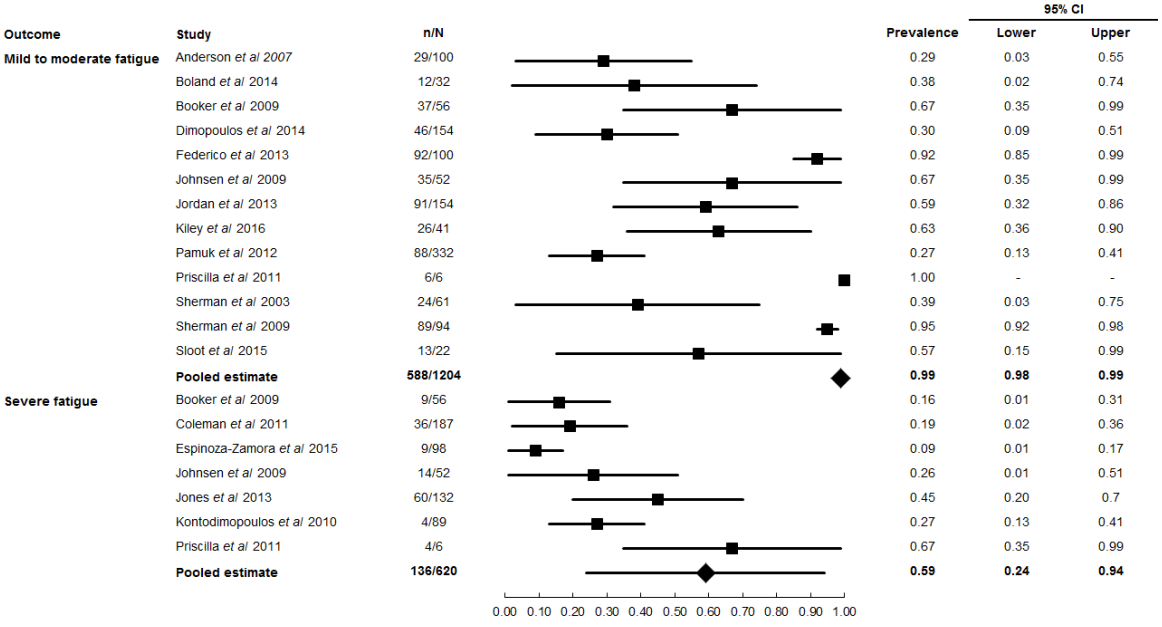
Concept			
Multiple myeloma	exp Multiple Myeloma/ exp Plasmacytoma/ myelom* plasm?cytom* plasmozytom* plasm* cell myelom* myelomatosis exp Leukemia, Plasma Cell/	plasm* adj3 neoplas* kahler* non-hodgkin*.mp. non adj2 hodgkin* NHL.ti. NHL.ab. autolog* auto-transplant*	bone marrow.mp. stemcell*.mp. Lymphoma, Non-Hodgkin/ Hematopoietic Stem Cell Transplantation/ Stem Cell Transplantation/ Bone Marrow Transplantation/
Symptoms	Symptoms Signs and symptoms/ Signs "Quality of Life"/ quality of life.mp. Health Status/ health status.mp. "Outcome Assessment (Health Care)"/ Pain / Fatigue / Tiredness Depressive disorders / Drowsiness Weakness Lack of energy Appetite / Anorexia /	Dyspnea / Dyspnoea Shortness of breath Breathlessness Depressed mood Sadness Hopelessness Anxiety / Nervousness Worrying Nausea / Vomiting / Sleeplessness Confusion / Delirium / Constipation / Obstipation Diarrhea /	Dry mouth Sore mouth Edema / Oedema Swelling Restlessness Dependent Loss of mobility Dysfunctional Cough / Discomfort Distress Social support / Spirituality / Spiritual Wellbeing
Prevalence	Cross-sectional Longitudinal Descriptive Prevalence Epidemiology Epidemiologic study	Incidence Frequency Burden Number Percentage	

Figure S1. Forest plot of the most common symptoms and problems in multiple myeloma with a pooled prevalence estimate of >50%. The final pooled logit was back transformed, resulting in pooled prevalence (proportions) and 95% confidence intervals.

Pain



Fatigue



Constipation

Outcome	Study	n/N	Prevalence	95% CI Lower	95% CI Upper
Mild to moderate constipation	Boland *et al* 2014	15/32	0.48	0.06	0.90
	Johnsen *et al* 2009	17/52	0.33	0.04	0.62
	Jordan *et al* 2013	43/154	0.28	0.08	0.48
	Kiley *et al* 2016	15/41	0.37	0.06	0.68
	Pamuk *et al* 2012	45/332	0.14	0.01	0.26
	Priscilla *et al* 2011	4/6	0.67	0.35	0.99
	Sloot *et al* 2015	18/22	0.81	0.63	0.99
	Pooled estimate	**157/639**	**0.67**	**0.24**	**0.93**
Severe constipation	Espinoza-Zamora *et al* 2015	34/98	0.35	0.08	0.62
	Johnsen *et al* 2009	6/52	0.11	0.01	0.21
	Kontodimopoulos *et al* 2010	9/89	0.10	0.01	0.19
	Priscilla *et al* 2011	3/6	0.50	0.07	0.93
	Pooled estimate	**52/245**	**0.45**	**0.05**	**0.93**

Tingling in the hands/feet

Outcome	Study	n/N	Prevalence	95% CI Lower	95% CI Upper
Tingling in the hands/feet	Jordan *et al* 2013	51/154	0.33	0.12	0.54
	Kiley *et al* 2016	25/41	0.61	0.23	0.99
	Molassiotis *et al* 2011	37/132	0.28	0.06	0.50
	Mols *et al* 2012	82/154	0.53	0.27	0.79
	Pooled estimate	**195/481**	**0.53**	**0.01**	**0.99**

Financial difficulties

Outcome	Study	n/N	Prevalence	95% CI Lower	95% CI Upper
Any financial difficulties	Johnsen et al 2009	16/52	0.31	0.05	0.57
	Kiley et al 2016	17/41	0.42	0.03	0.81
	McQuellon et al 2010	18/55	0.33	0.03	0.63
	Pamuk et al 2012	243/332	0.73	0.50	0.96
	Priscilla et al 2011	5/6	0.83	0.81	0.85
	Pooled estimate	**299/486**	**0.79**	**0.62**	**0.96**
Severe financial difficulties	Espinoza-Zamora *et al* 2015	20/98	0.20	0.04	0.36
	Johnsen *et al* 2009	5/52	0.09	0.01	0.17
	Kontodimopoulos *et al* 2010	1/89	0.01	0	0.02
	Priscilla *et al* 2011	3/6	0.77	0.55	0.99
	Pooled estimate	**29/245**	**0.43**	**0.04**	**0.82**

Table S2. Change in symptom prevalence and quality of life over time in included longitudinal studies

Symptom	Study	Time point	Prevalence
Pain	**Anderson *et al* 2007 (17)**	Baseline	21.0
		Conditioning	12.0
		At transplant	11.0
		At nadir	27.0
		30 days post transplant	9.0
	Coleman *et al* 2002 (38)	Baseline	17.0
		At transplant	9.2
		6 days post transplant	26.4
		12 days post transplant	8.1
	Jones *et al* 2013 (21)	Pre transplant	35.9
		Post transplant	42.0
	Sherman *et al* 2009 (60)	Pre transplant	39.0
		Post transplant	30.9
Bone aches	**Jones *et al* 2013 (21)**	Pre transplant	18.0
		Post transplant	19.0
Fatigue	**Anderson *et al* 2007 (17)**	Baseline	29.0
		Conditioning	22.0
		At transplant	32.0
		At nadir	55.0
		30 days post transplant	34.0
	Jones *et al* 2013 (21)	Pre transplant	45.3
		Post transplant	68.0
	Sherman *et al* 2009 (60)	Pre transplant	94.7
		Post transplant	89.4
Weakness	**Anderson *et al* 2007 (17)**	Baseline	14.0
		Conditioning	13.0
		At transplant	23.0
		At nadir	52.0
		30 days post transplant	31.0
	Jones *et al* 2013 (21)	Pre transplant	18.0
		Post transplant	38.0
Sleep problems	**Anderson *et al* 2007 (17)**	Baseline	8.0
		Conditioning	34.0
		At transplant	26.0
		At nadir	39.0
		30 days post transplant	14.0
	Jones *et al* 2013 (21)	Pre transplant	18.0
		Post transplant	40.0
Feeling sick	**Anderson *et al* 2007 (17)**	Baseline	5.0
		Conditioning	9.0
		At transplant	22.0
		At nadir	42.0
		30 days post transplant	9.0
Drowsiness	**Jones *et al* 2013 (21)**	Pre transplant	16.0
		Post transplant	44.0

Appetite loss	**Anderson *et al* 2007 (17)**	Baseline	5.0
		Conditioning	22.0
		At transplant	34.0
		At nadir	56.0
		30 days post transplant	11.0
Nausea/vomiting	**Anderson *et al* 2007 (17)**	Baseline	3.0
		Conditioning	14.0
		At transplant	25.0
		At nadir	35.0
		30 days post transplant	6.0
	Coleman *et al* 2002 (38)	Baseline	11.9
		At transplant	35.6
		6 days post transplant	33.3
		12 days post transplant	9.2
Diarrhoea	**Anderson *et al* 2007 (17)**	Baseline	2.0
		Conditioning	5.0
		At transplant	9.0
		At nadir	34.0
		30 days post transplant	2.0
	Coleman *et al* 2002 (38)	Baseline	1.2
		At transplant	5.8
		6 days post transplant	23.0
		12 days post transplant	20.7
Breathlessness	**Anderson *et al* 2007 (17)**	Baseline	10.0
		Conditioning	6.0
		At transplant	4.0
		At nadir	16.0
		30 days post transplant	8.0
Mouth problems	**Anderson *et al* 2007 (17)**	Baseline	2.0
		Conditioning	1.0
		At transplant	0.0
		At nadir	17.0
		30 days post transplant	1.0
	Jones *et al* 2013 (21)	Pre transplant	8.0
		Post transplant	57.0
Distress	**Anderson *et al* 2007 (17)**	Baseline	17.0
		Conditioning	9.0
		At transplant	14.0
		At nadir	20.0
		30 days post transplant	10.0
	Bergerot *et al* 2015 (33)	Baseline	60.0
		2.5 months post start chemotherapy	40.0
		Last day of chemotherapy	0.0
Anxiety	**Bergerot *et al* 2015 (33)**	Baseline	60.0
		2.5 months post start chemotherapy	40.0
		Last day of chemotherapy	0.0

	Pillay *et al* 2015 (54)	Pre transplant	18.3
		2-3 weeks post transplant	13.3
		3 months post transplant	8.3
	Sherman *et al* 2009 (60)	Pre transplant	39.4
		Post transplant	44.7
Depression	**Anderson *et al* 2007 (17)**	Baseline	13.0
		Conditioning	7.0
		At transplant	7.0
		At nadir	16.0
		30 days post transplant	5.0
	Bergerot *et al* 2015 (33)	Baseline	60.0
		2.5 months post start chemotherapy	20.0
		Last day of chemotherapy	0.0
	Campbell *et al* 2011 (37)	At hospital admission	23.0
		At discharge	37.0
		3 months post transplant	27.0
		6 months post transplant	26.0
		12 months post transplant	23.0
	Pillay *et al* 2015 (54)	Pre transplant	8.3
		2-3 weeks post transplant	13.3
		3 months post transplant	8.3
	Sherman *et al* 2009 (60)	Pre transplant	40.4
		Post transplant	48.4
Quality of life problems			
Decreased physical functioning	**Pillay *et al* 2015 (54)**	Pre transplant	60.0
		2-3 weeks post transplant	85.1
		3 months post transplant	47.5
	Sherman *et al* 2009 (60)	Pre transplant	70.2
		Post transplant	43.6
Decreased role functioning	**Pillay *et al* 2015 (54)**	Pre transplant	23.3
		2-3 weeks post transplant	70.2
		3 months post transplant	35.0
	Sherman *et al* 2009 (60)	Pre transplant	57.5
		Post transplant	67.0
Decreased emotional functioning	**Pillay *et al* 2015 (54)**	Pre transplant	40.0
		2-3 weeks post transplant	29.8
		3 months post transplant	25.0
	Sherman *et al* 2009 (60)	Pre transplant	19.2
		Post transplant	16.0
Decreased social functioning	**Pillay *et al* 2015 (54)**	Pre transplant	1.7
		2-3 weeks post transplant	6.4
		3 months post transplant	2.5
	Sherman *et al* 2009 (60)	Pre transplant	2.1
		Post transplant	3.2

Erratum to: Prevalence of symptoms in patients with multiple myeloma – a systematic review and meta-analysis

The following table presents the re-calculated meta-analytic results originally presented in Table 2 on page 424 of the article. The decision to re-analyse the results was made after checking the results and forest plots of the original meta-analysis and noticing the biasing effect of small study estimates from Priscilla et al. (2011) (1) and Federico et al. (2013) (2). This was pointed out by the examiners of the thesis. The bias in the analysis should have been picked up before publication, as the forest plots presented in the supplementary appendix to the paper clearly show a problem with the pooling of individual prevalences. This was a learning point for me, to use visualisations of analysis results and how this can help to check results for common sense.

The most likely cause for this bias was in the incorrect pooling of estimates under the random effects model using the generic inverse variance weighting technique applied within the SPSS macro provided by Lipsey & Wilson (2001) (3). Although the use of the SPSS macro is not fully detailed in the paper, it was in the thesis.Therefore, all meta-analyses of prevalence of symptoms and quality of life problems were re-calculated with forest plots redrawn using the 'meta' package in R (Schwarzer, 2015) (4). These results are presented in the following table. The forest plots originally presented in Figure S1 of the "Supplemental material" appendix are included subsequent to Table 2. For meta-analysis, the same technique of logit transformation was followed. However, confidence intervals are calculated using normal approximation as available within the R package meta.

References:

(1) Priscilla D, Hamidin A, Azhar MZ, Noorjan KON, Salmiah MS, Bahariah K. Quality of life among patients with hematological cancer in a Malaysian hospital. Medical Journal of Malaysia. 2011; 66: 117-120.

(2) Federico V, Cartoni C, Levi A, Meloni E, Gentilini F, Biagioli G, Finsinger P, Foa R, Petrucci MT. Evaluation of symptom assessment and health-related quality of life in MM patients followed in simultaneous care. Clinical Lymphoma, Myeloma & Leukemia. 2013; 14: 237.

(3) Lipsey MW, Wilson DB. Practical meta-analysis. Thousand Oaks: Sage; 2001.

(4) Schwarzer G. meta: General package for meta-analysis. 2015. Available at: https://cran.r-project.org/web/packages/meta/index.htm. Accessed on 08/05/2017.

Table 2 Prevalence of symptoms and quality of life problems

Symptom	# of studies	# of subjects	Original Prevalence (%)	95% CI LB	95% CI UB	New logit transformation Prevalence (%)	LB	UB	I^2 (%)
Pain	15	1882	**58.6**	8.8	95.2	**44.5**	34.4	54.9	94
Severe pain	10	1136	**44.7**	2.2	96.7	**25.9**	18.2	35.6	91
Bone aches	4	572	**41.0**	0,0	100.0	**38.8**	24.9	54.9	94
Fatigue	13	1204	**98.8**	98.1	99.2	**59.3**	44.8	72.3	97
Severe fatigue	7	620	**59.7**	12.9	93.7	**20.7**	11.1	35.4	93
Weakness	3	264	**21.6**	0.1	99.7	**17.7**	13.4	23.0	2
Tiredness	3	318	**46.9**	0.2	99.7	**39.7**	33.6	46.1	19
Sleep problems	11	1075	**34.5**	3.8	87.4	**28.7**	20.9	37.9	87
Severe sleep problems	4	245	**32.1**	1.9	92.1	**25.9**	8.4	57.3	94
Feeling sick	2	254	**13.5**	0.0	100.0	**13.9**	1.9	57.0	97
Dizziness	3	428	**36.8**	0.2	99.5	**32.7**	16.0	55.3	94
Drowsiness	3	308	**40.6**	0.3	99.4	**32.5**	14.0	58.9	94
Appetite loss	8	770	**42.7**	5.3	90.8	**23.1**	11.4	41.1	95
Severe appetite	4	245	**32.8**	2.0	92.2	**25.7**	6.5	63.2	96
Nausea	4	541	**16.9**	0.1	99.0	**8.5**	4.1	16.8	72
Vomiting	2	109	**9.5**	0.1	99.4	**4.6**	0.4	38.1	81
Nausea/vomiting	10	981	**17.7**	1.1	80.5	**13.3**	3.2	41.5	97
Severe nausea/vomiting	4	245	**2.7**	0.1	59.7	**9.2**	0.5	66.9	98
Diarrhoea	8	805	**40.7**	4.8	90.4	**9.5**	2.1	33.9	96
Severe diarrhoea	4	245	**21.1**	0.8	89.9	**15.3**	1.4	70.3	98
Constipation	7	639	**66.5**	23.5	92.8	**39.1**	24.3	56.3	92
Severe constipation	4	245	**45.2**	4.6	93.4	**21.3**	9.0	42.5	87
Breathlessness	7	540	**36.6**	3.3	90.7	**32.6**	17.9	51.8	95
Severe breathlessness	4	245	**33.0**	1.8	92.2	**25.1**	5.0	67.9	97
Cough*	1	253	**42.0**	23.9	60.0	-	-	-	-
Mouth problems	7	1047	**21.4**	0.1	98.3	**22.5**	13.8	34.5	96
Severe mouth problems*	1	154	**17.1**	1.4	35.6	-	-	-	-
Memory problems	3	281	**42.6**	0.1	99.9	**37.0**	21.3	55.9	90
Difficulty paying attention*	1	100	**8.0**	1.3	29.1	-	-	-	-
Tingling in hands/feet	4	481	**53.4**	0.4	99.7	**42.7**	29.0	57.7	90
Severe tingling*	1	154	**32.0**	10.8	53.1	-	-	-	-
Distress	4	379	**27.8**	0.0	100.0	**30.4**	19.3	44.5	82
Anxiety	10	835	**35.7**	1.0	96.9	**29.8**	21.0	40.3	89
Case of anxiety	8	720	**26.7**	0.2	98.4	**26.4**	19.1	35.3	84
Depression	11	1028	**22.3**	0.3	96.2	**19.2**	13.1	27.1	87
Case of depression	9	774	**23.6**	0.3	97.3	**20.8**	13.4	31.0	89
Sexual problems	3	115	**23.5**	0.2	98.1	**29.0**	19.0	41.6	51
Muscle cramps	2	176	**6.9**	0.0	99.5	**15.6**	2.1	61.5	91
Peripheral edema	2	176	**6.5**	0.0	99.5	**14.5**	0.6	41.7	87
QOL problems									
Decreased physical functioning	13	1424	**98.9**	98.2	99.3	**43.2**	33.3	53.6	96.3
Severely decreased PF	4	245	**27.3**	1.4	91.1	**8.6**	2.8	24.0	80
Decreased role functioning	9	941	**67.0**	21.2	93.9	**41.6**	26.5	58.3	96
Severely decreased RF	4	245	**46.7**	5.0	93.6	**24.2**	9.9	48.1	88
Decreased emotional functioning	9	1005	**57.7**	12.5	92.9	**21.1**	14.7	29.2	92
Severely decreased EF	4	245	**26.3**	1.3	90.8	**6.0**	1.8	18.3	60
Decreased cognitive functioning	5	577	**80.2**	40.0	96.1	**13.8**	4.7	34.0	94
Severely decreased CF	4	245	**14.1**	0.4	87.2	**5.4**	1.3	20.1	79
Decreased social functioning	8	855	**58.0**	12.2	93.2	**15.8**	8.2	28.5	96
Severely decreased SF	4	245	**28.6**	1.5	91.5	**10.7**	4.1	25.1	74
Severe disease symptoms	2	187	**1.5**	0.0	100.0	**1.6**	0.5	4.9	0

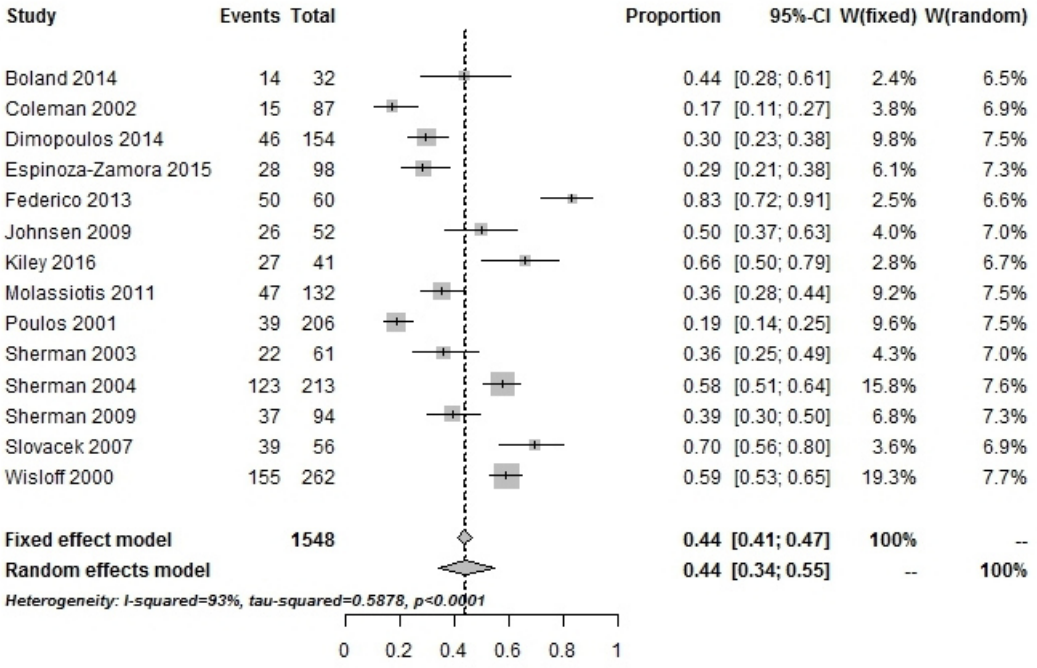
Symptom	# of studies	# of subjects	Original Prevalence (%)	95% CI LB	95% CI UB	New logit transformation Prevalence (%)	LB	UB	I^2 (%)
Most severe side effects	3	219	**15.1**	0.0	99.5	**4.2**	0.2	47.5	93
Worry about dying/future	6	569	**49.7**	1.1	98.9	**31.8**	13.4	58.4	98
Severe worry about dying	3	341	**11.9**	0.0	100.0	**11.9**	2.3	43.2	97
Problems with body image	3	228	**41.3**	0.1	99.7	**18.9**	3.5	59.9	96
Financial difficulties	7	673	**78.4**	39.1	95.4	**34.1**	15.6	59.2	98
Severe financial difficulties	4	245	**43.3**	4.2	93.1	**13.3**	4.4	33.6	90

*No pooled prevalence (only one study).
CF cognitive functioning, EF emotional functioning, PF physical functioning, RF role functioning, SF social functioning

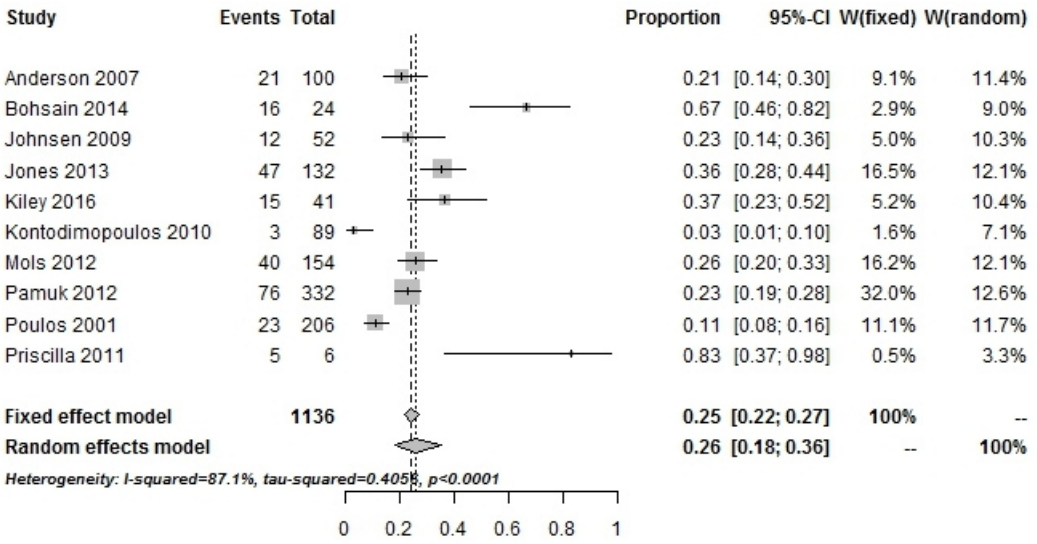
Supplemental material:

Figure S1. Forest plot of the most common symptoms and problems in multiple myeloma. The final pooled logit was back transformed, resulting in pooled prevalence (proportions) and 95% confidence intervals.

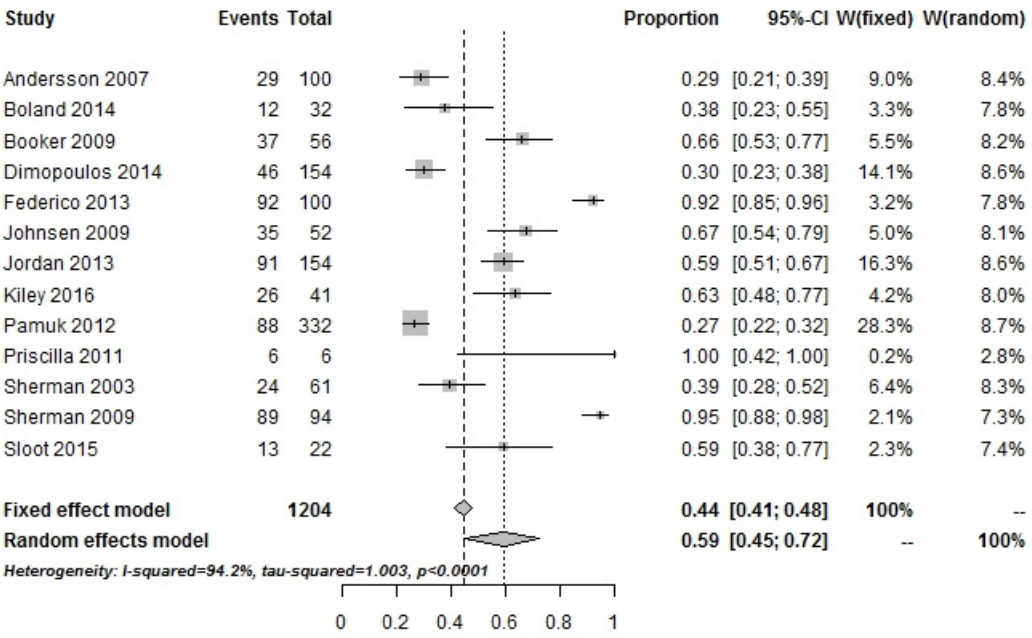
Pain



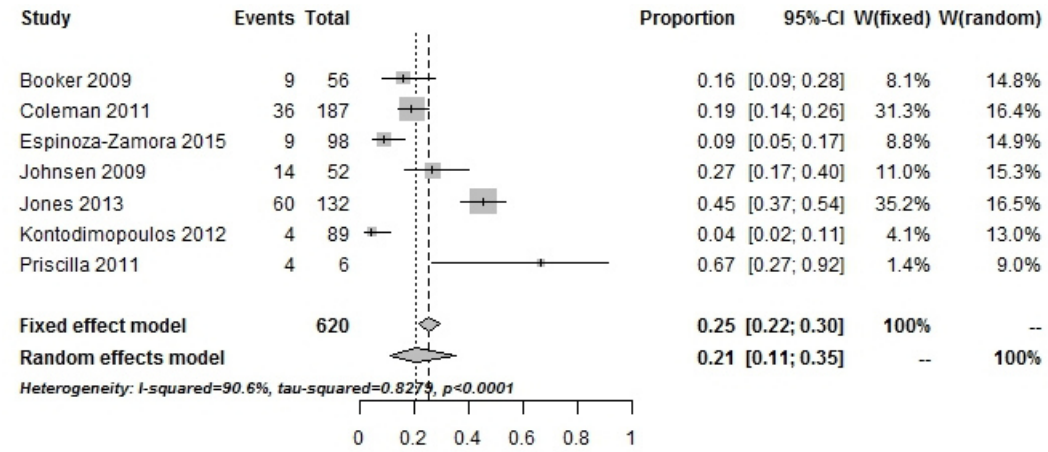
Severe pain



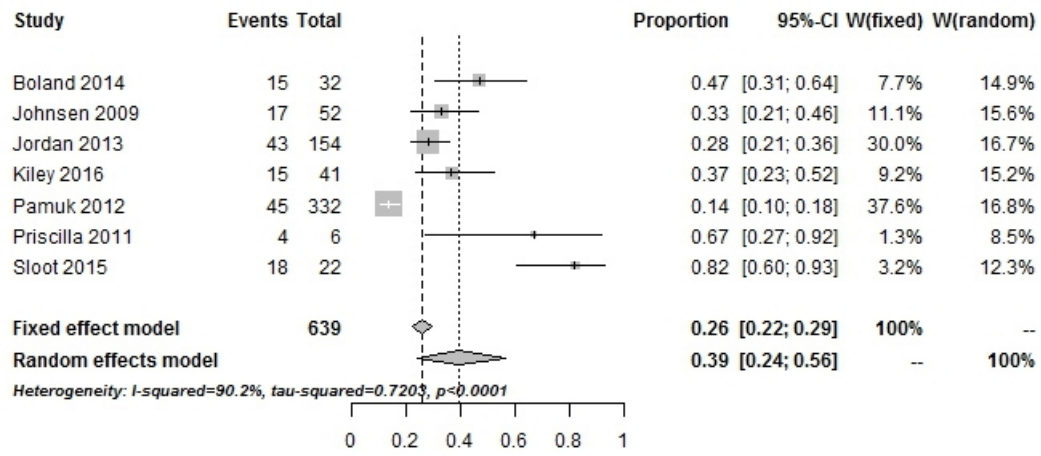
Fatigue



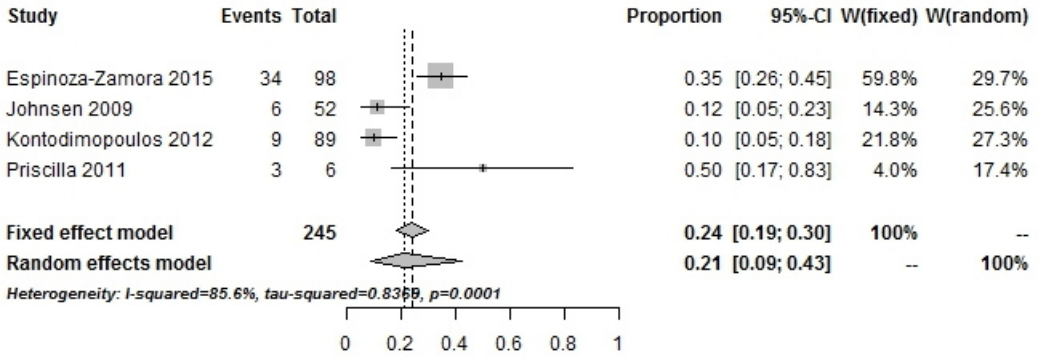
Severe fatigue



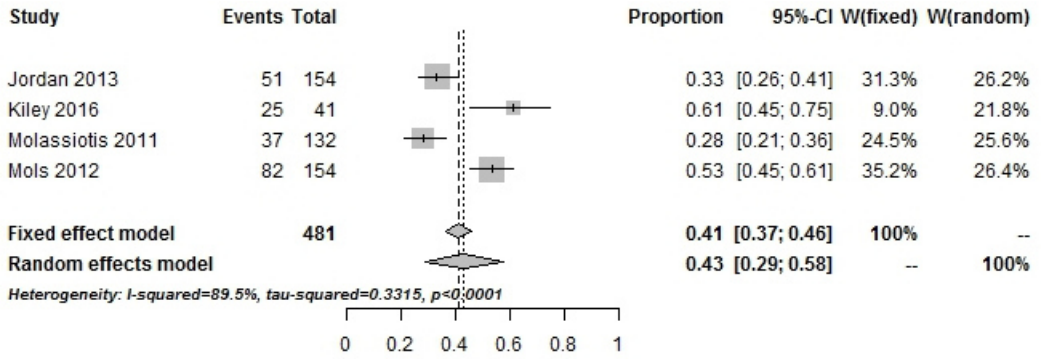
Constipation



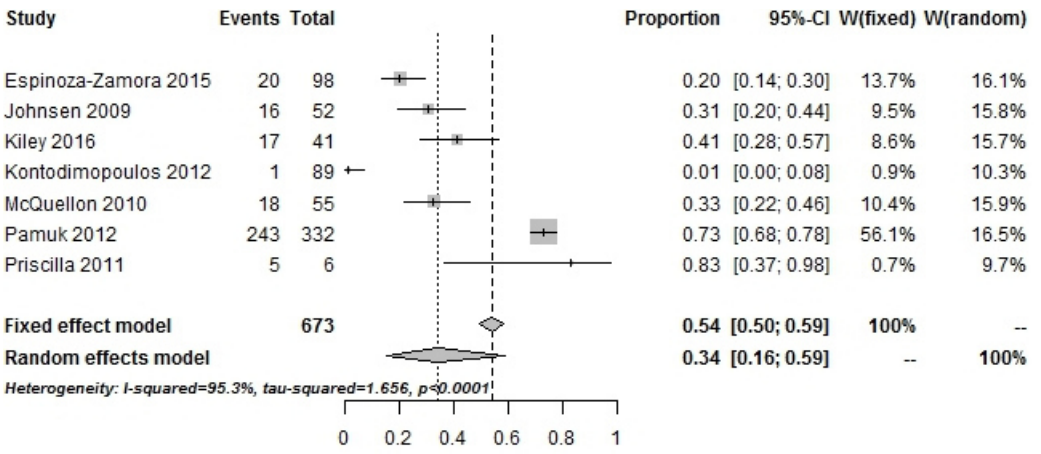
Severe constipation



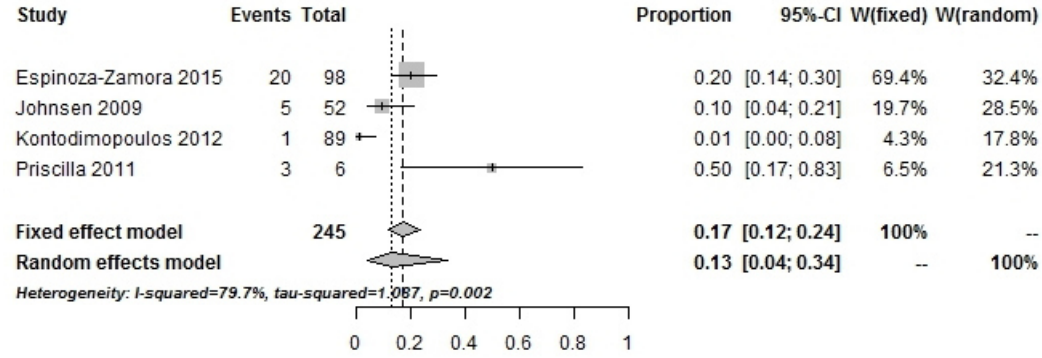
Tingling in the hands/feet



Financial difficulties



Severe financial difficulties



2.2.2.2 Longitudinal quality of life in multiple myeloma

Although symptom prevalence has been studied in a variety of multiple myeloma samples and in various settings (369), and multiple myeloma is increasingly becoming a chronic cancer with many patients living years with their disease, longitudinal studies examining changes in QOL and its component parts are rare. Table 2 lists the available evidence from clinical trials, studies in ASCT populations and observational studies in multiple myeloma. All longitudinal evidence stemming from mixed populations was excluded since multiple myeloma is a unique blood cancer with a specific profile of QOL and symptom burden (27,88).

Despite the call for inclusion of QOL as a standard secondary endpoint in clinical trials (287), HRQOL as endpoints were only included in a few randomised controlled phase II and phase III trials in multiple myeloma (see Table 2) (23,82,365,366,370-377). Almost all of these trials reported an improvement of QOL or its component scores over the course of treatment with single or combination drug anti-myeloma regimens. One exception is the phase III trial by Dimopoulos and coauthors (2013,2014) (373,374). The authors reported a worsening of physical functioning but improvement or stabilisation of general QOL in a sample of newly diagnosed multiple myeloma patients. It is not possible to extrapolate a common QOL trajectory from this data since clinical trial samples are usually selected according to narrowly defined eligibility criteria and may exclude elderly patients with comorbidities, a group that constitutes the majority of myeloma patients (58,145,147,148).

Four studies followed newly diagnosed patients and patients with relapsed or refractory disease for up to 3 years after autologous stem cell transplantation (32,33,35,378). Except for the newest observational study by Wang and co-authors (2015) (379), all of these studies included a baseline pre-transplantation. Two studies utilised data from clinical trials and presented secondary, separate analyses of QOL data (32,378). Except for Sherman et al. (2009a,b) (33,35), they reported transient increases in symptom burden and QOL impairment that lasted a maximum of six months after the procedure (32,378). Campagnaro et al. (2008) (378) described an even earlier recovery of symptom burden after the nadir of counts was reached. Wang et al. (2015) (379), tracking prevalence of symptoms over a period of 3 to 9 months post ASCT, contradicted this finding by showing that more than a third of the sample experienced a continuously high symptom burden with several symptoms, among them fatigue, pain, peripheral neuropathy and bone aches. However, the authors did not describe corresponding QOL trajectories in their sample and focused on point prevalence at each assessment time point instead. Sherman et al. (2009a,b) (33,35) observed a deterioration of overall QOL scores in their longitudinal study following 94

Table 2: Longitudinal health-related QOL data in multiple myeloma (100%), (a) clinical trials, (b) stem cell transplantation samples (SCT), (c) observational studies.

Study (year)	Treatments/ sample	QOL instruments	QOL results
(a) Clinical trials			
Verelst et al. (2011) (370) HOVON 49 trial	MP (n = 168) vs MPT-T (n = 165), NDMM	QLQ-C30 QLQ-MY24	Equal improvement of QOL
Waage et al. (2010) (371) NMSG trial	MP (n = 175) vs MPT (n = 182), NDMM	QLQ-C30	Equal QOL improvement in both arms
Delforge et al. (2012) (365) VISTA trial	MP (n = 338) vs VMP (n = 344), NDMM	QLQ-C30	Better QOL with once-weekly bortezomib, initial deterioration and above-baseline levels post-tx
Niesvisky et al. (2013) (372) UPFRONT trial	VD (n = 100) vs VTD (n = 100) vs VMP (n = 100), NDMM	QLQ-C30	Transient decrease in QOL in all arms during induction, improvement or stabilization during V-maintenance
Dimopoulos et al. (2013, 2014) (373,374) MM015-trial	MP (n = 154) vs MPR (n = 153) vs MPR + R-maintenance (n = 152) NDMM	QLQ-C30 QLQ-MY20	Improvement of QOL during induction, thereafter stabilization of QOL, worsening of physical functioning
Delforge et al. (2015) (366) FIRST trial	Rd 18 cycles (n = 541) or continuous till PD (n = 535) vs MPT (n = 547), NDMM	QLQ-C30 QLQ-MY20 EQ-5D	Equal improvement for preselected domains: pain, fatigue, disease symptoms, physical functioning, global health scale
Dubois et al. (2006) (23) SUMMIT-trial	V monotherapy, If PD or stable disease after cycle 4: V plus D (n = 144), RRMM	QLQ-C30 QLQ-MY24 FACIT Fatigue FACT-NTx	Fatigue scores improved in responders with a positive correlation between QOL and Fatigue
Lee et al. (2008) (375) APEX-trial	V (n = 296) vs D (n = 302), RRMM	QLQ-C30 FACT-NTx	With V better FACT-NTx scores and better QOL compared to D
Hjorth et al. (2012) (376) NSMG trial	In M-refractory: TD (n = 67) vs VD (n = 64), RRMM	QLQ-C30	No QOL improvement over time in both arms
Alegre et al. (2012) (377) MM-018 trial	R + High dose D (n = 63), RRMM	QLQ-C30 QLQ-MY20	Improvement in future perspective score, no other significant changes in QOL
Weisel et al. (2015) (82) MM-003 trial	In V- and R refractory patients: Pom+Low dose Dex (n = 302) vs D (n = 153) RRMM	QLQ-C30 QLQ-MY20 EQ-5D	Favorable trends for 7/8 pre-selected QOL domains in Pom-Dex-group (global health, side effects of treatment, physical/ emotional functioning, pain, fatigue, health utility)
(b) ASCT			
Campagnaro et al. (2008) (378) 3 years	64 NDMM and RRMM undergoing HDC + ASCT	MDASI-BMT	Symptom burden increase from baseline to nadir of counts, majority returning to baseline by Day 30
Gulbrandsen et al. (2001) (32) 3 years	Secondary analysis of RCT HDC + ASCT (n = 334)	QLQ-C30	Improvement in global QOL until 6 months follow-up, only small trend towards better physical functioning at 3 years, all domain scores improve after 6 months except for emotional functioning
Sherman et al. (2009a,b) (33,35) 3 months	Observational study of 94 NDMM	FACT-G FACT-BMT	Deterioration of FACT-BMT and depression and life satisfaction scores over 3 months

Wang et al. (2015) (379) 6 months	Observational study 3 months post ASCT (n = 51)	QLQ-C30 MDASI-MM	35% in high symptom group throughout 6 months follow-up, highest symptom ratings for fatigue, pain, numbness, bone aches and muscle weakness
(c) Observational studies			
Delforge et al. (2009) (380) Follow-up not reported	103 RRMM undergoing bortezomib tx	QLQ-C30	Small but significant deterioration in physical, role, emotional, cognitive, social funtioning
Mols et al. (2012) (381) 1 year	156 NDMM and RRMM from population registry	QLQ-C30 QLQ-MY20	Worsening of QOL, fatigue, nausea/vomiting, pain and dyspnoea over one year

ASCT, autologous stem cell transplantation, D, dexamethasone, EQ-5D, EuroQOL -5D, FACT-BMT, Functional Assessment of Cancer Therapy Bone Marrow Transplantation module, FACT-G, Functional Assessment of Cancer Therapy General , questionnaire, FACT-NTx, Functional Assessment of Cancer Therapy chemotherapy-related side effects questionnaire, HDC, high dose chemotherapy, M, melphalan, MDASI-BMT, M.D. Anderson Symptom Inventory Bone Marrow Transplantation module, NDMM, newly diagnosed multiple myeloma, P, prednisone, PD, progressive disease, Pom, pomalidomide, QLQ-C30, EORTC quality of life questionnaire C30, QLQ-MY, EORTC quality of life questionnaire myeloma module, QOL, quality of life, R, Revlimid, RCT, randomised controlled trial, Rd, Revlimid maintenance, RRMM, relapsed refractory multiple myeloma, T, thalidomide, V, Velcade

newly diagnosed multiple myeloma patients. They also reported a worsening of depression and anxiety over this time period. Again, generalising from ASCT populations to how QOL might change over time in multiple myeloma is difficult due to the selected nature of individuals in these studies (145). This is true for all treatment-defined samples (380).

Only one observational study employing a population perspective was published by a group from the Netherlands using data from the Eindhoven Cancer Registry (381). In this prospective study, the EORTC QLQ-C30 together with its myeloma module was sent to 156 patients who had been diagnosed with myeloma from 1999 to 2010. Two questionnaire packs were sent one year apart to derive one-year follow-up scores of symptoms and disease-specific complaints. Statistically significant and clinically relevant (using minimal important differences, MIDs, derived by Kvam and co-authors (368,382,383)) worse scores, compared to a norm population, were observed on all QLQ-C30 subscales at both time points. For the analysis of changes over time, the final sample was considerably smaller (n = 80). Sixty-five up to 90% of patients reported a deterioration of functioning and/or symptom subscales with the most prominent worsening reported for fatigue, nausea and vomiting, pain and dyspnoea (381). The study demonstrates the considerable disease burden which is present for patients regardless their stage of disease or the time elapsed since diagnosis.

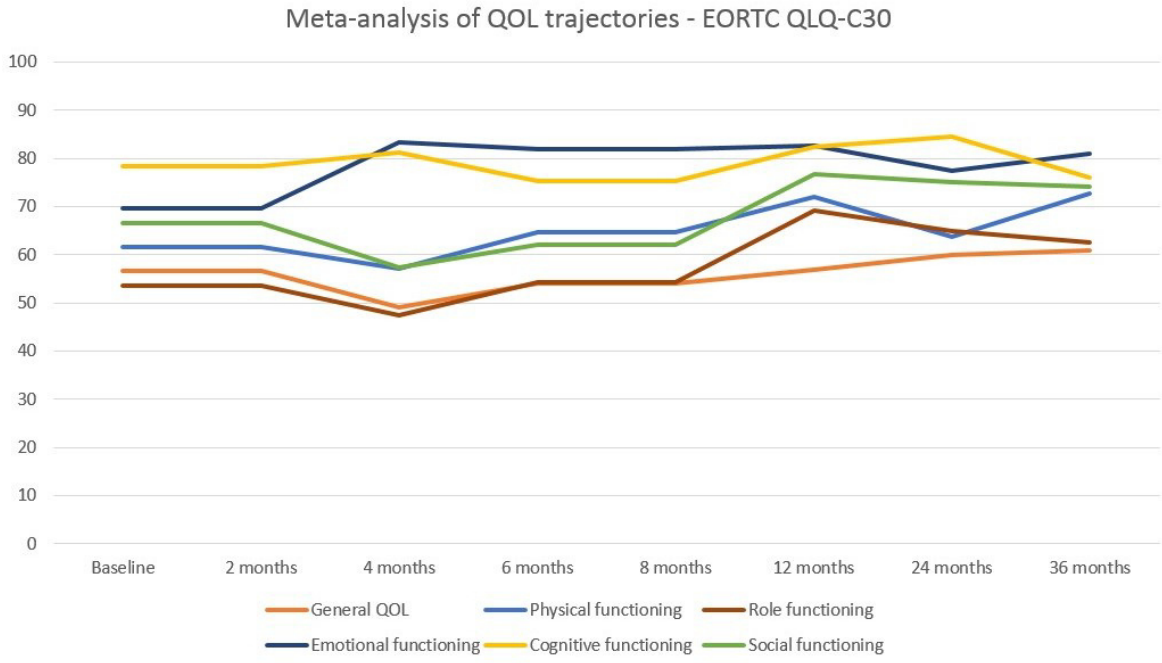
To glean more information on how QOL scores change over time, results from the EORTC QLQ-C30 and its subscales were graphed for all longitudinal studies listed in Table 2. These trajectories can be seen in Figure 5. The first figure shows all subscales from the EORTC QLQ-C30. Since these are subscales of functioning, a higher value indicates better functioning or QOL. The second

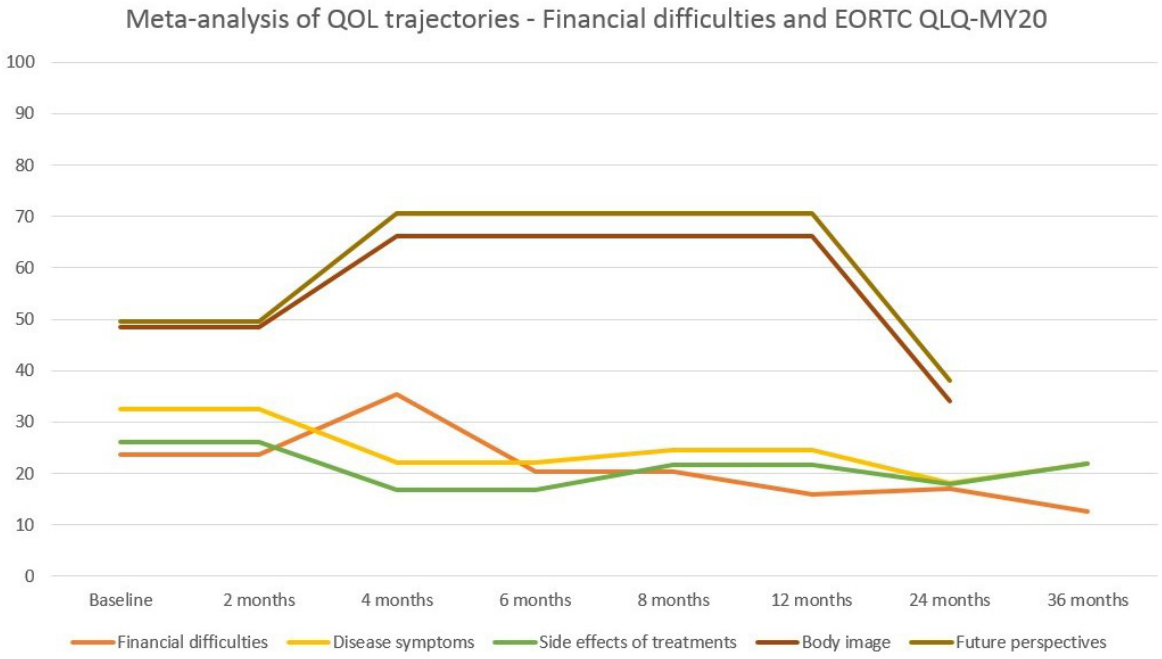
panel shows trajectories of disease-specific subscales. These are interpreted differently, with higher values signifying more disease-specific symptoms and complaints in the different domains. Since financial difficulties have been reported as one of the major problems in multiple myeloma (358,384,385), the QLQ-C30 subscale 'Financial difficulties' was also graphed. Overall, general QOL and emotional functioning seem to be the domain with the most complaints over time, followed by physical functioning and social functioning. A worsening of functioning scores up to 4 months is seen, with gradual but heterogeneous recovery of scores. A similar picture is present for disease-specific subscales, except for body image and future perspectives subscales. These show a high level of severity throughout. However, it must be kept in mind that this data largely stems from ASCT studies and randomised controlled trials and trajectories observed might be a direct reflection of treatment-related patterns. Synthesising information from these studies should be interpreted with caution because of the considerable heterogeneity within this comparison. Also, mean trajectories can obscure aberrant change scores and lead to the assumption of a more homogeneous picture with not much fluctuation despite the existence of subgroups that might experience a very different trajectory than the depicted mean trajectory (386).

To sum up, the evidence on how QOL changes over time in multiple myeloma is scarce with only one study employing a true population perspective and remaining studies using treatment-defined samples. The study by Mols et al. (2012) (381) only used two time points and this does not provide a clear picture of the change in experiences of patients. QOL scores reflect the course of treatment with many patients seemingly reporting a recovery and improvement in QOL and its domains at month four to six post autologous stem cell transplantation. Evidence on changes in QOL in later stages of disease and the existence of subgroups within the relative heterogeneous group of myeloma patients have not been explored. For generalisability/external validity, a study is needed that does not recruit patients that are defined by the treatment regimen they receive.

The last section within this chapter on symptom burden and QOL in multiple myeloma reviews the factors that are associated with a poor QOL in this disease. For this analysis, data from all studies reporting cross-sectional or longitudinal studies was pooled and regression or correlation coefficients between independent variables (demographic characteristics, clinical and disease characteristics, symptom burden, stage of illness etc.) and the outcome were subjected to a meta-analysis. This analysis was submitted as a paper to the European Journal of Cancer.

Figure 5: Comparison of findings from this study to QOL meta-analysis: severity of symptoms, QOL functioning and myeloma-specific QOL problems (EORTC QLQ-C30 and QLQ-MY20)





2.2.2.3 Factors associated with health-related quality of life in multiple myeloma: a systematic review and meta-analysis

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Abstract

Multiple myeloma is associated with a higher burden of disease than other haematological cancers. To target services towards those in need of support, we need to understand who is at risk of developing poor health-related quality of life (HRQOL). We conducted a summary-data meta-analysis to systematically review, assess and analyse the strength of association between demographic, disease and treatment-related factors and HRQOL in multiple myeloma. We searched Medline, Embase, PsycINFO, Cinahl, Assia, the Cochrane library and NHS EED databases, journals and citations. Two independent raters reviewed abstract and full-texts. Meta-analysis used Fisher's z method for Pearson correlations (effect size), inverse variance weighting and random effects per factor. Of 15,083 references, 34 studies totalling 6,794 participants were included. The largest effect sizes were found for nutritional risk (r=-0.54, 95% CI -0.73 to -0.35), fatigue (r=-0.52, 95% CI -0.57 to -0.47), and pain (r=-0.45, 95% CI -0.5 to -0.39). Medium associations were reported for symptoms and physiological parameters, e.g. M-protein level, and cytokines. High hemoglobin was a moderate protective factor for HRQOL (r=0.39, 95% CI 0.33 to 0.44). Demographic, disease- and treatment-related factors showed weak associations only, except for response to treatment (achieving at least a partial response: r = 0.29, 95%CI 0.24 to 0.34). Early detection of those at risk for developing poor HRQOL should consider symptoms as well as biochemical factors and cannot focus on response to treatment or assessment of paraprotein alone. Regular measurement of symptoms can help screen for those with poor QOL.

Keywords: Multiple Myeloma; Quality of Life; Outcome Assessment; Systematic Review

Introduction

Multiple myeloma is the second most common hematological malignancy in the UK [1], an incurable cancer of the bone marrow that affects mainly older people, with a median age at diagnosis of 70-74 years [2]. As such, multiple myeloma is an example for the changing face of cancer, as a condition that may be managed as a chronic illness with a recurrent pattern of treatments followed by maintenance therapy [3]. Front-line treatment with high-dose chemotherapy and transplant has improved median survival for those under the age of 65 to five years or longer [1].

These improvements in survival time and duration of response have led to a need to evaluate and better understand patient-reported outcomes such as health-related quality of life (HRQOL), to capture benefits and adverse effects alongside traditionally used parameters such as response to treatment and toxicity profiles. There is evidence that HRQOL is substantially impaired in myeloma with patients suffering more symptoms and problems than in other haematological cancers [4] and through all phases of their disease [5]. HRQOL has also been shown to be a predictor for survival alongside clinical parameters [6]. In addition to the disease and its treatment affecting daily life, the economic burden of multiple myeloma is among the highest compared to all cancers [7], due to treatment, supportive and indirect societal costs.

Identifying determinants of poor outcome can help target services to those individuals most at risk [8]. This can help to identify prognostic indicators and planning of early and preventive interventions. Focusing on what predicts poor HRQOL also helps to bring a patient-centred perspective into care in a condition that is long-lasting and incurable. To date, reviews examining correlates of QOL have focused either on treatment populations or mixed haematological samples [9-14], and have provided a narrative synthesis but have not determined the relative strength of association between determinants and outcomes. Therefore, there is controversy in the literature regarding the impact of various socio-demographic (e.g. age, ethnicity), disease (e.g. length of survival, phase of disease) and treatment factors (e.g. receiving specific types of chemotherapy) in terms of weak or inconclusive evidence [9,11,13].

Knowledge of the factors that are associated consistently and strongly with the outcome poor QOL can help focus assessment in clinical trials and in routine clinical practice towards those variables that act as risk factors [15,16].

The aim of this meta-analysis is to assess the strength of association between demographic, disease, treatment and psychosocial factors with HRQOL to understand which myeloma patients are most at risk of a poor outcome.

Methods

The design of this study is a systematic literature review with meta-analysis following the PRISMA guidance [17].

Searches

The online databases Ovid Medline, Embase, PsycINFO, Ebscohost CINAHL, ProQuest ASSIA, the Cochrane Library and Centre for Reviews and Dissemination NHS Economic Evaluations database were searched from their inception to March 2015. The search was supplemented by contacting authors, hand-searching bibliographies of reviews on HRQOL in myeloma [9-14], key journals (Quality of Life Research, European Journal of Haematology, Blood, Bone Marrow Transplantation, Biology of Blood and Marrow Transplantation, British Journal of Haematology, Psycho-Oncology), citation and reference searches and a Web of Science search for conference abstracts. Grey literature was not searched because the majority of ongoing studies could likely be identified through databases and searches for conference abstracts [18]. (For search strategy see Online Appendix A)

Study selection

Published studies were considered if they met the following eligibility criteria:

(a) Adult (≥18 years) homogeneous or mixed samples including at least 50% of patients with multiple myeloma of all disease stages on- or off-treatment. This cut-off was used to ensure an adequate relevance and specificity of the results to myeloma;

(b) Outcomes assessed being either HRQOL, measured by using a single global item, a subscale or a total score from a validated HRQOL measure. In addition, distress was included as a proxy for HRQOL in the systematic review but not the meta-analysis, measured by any validated tool;

(c) Statistical analysis producing an estimate of the association of the independent (IV) with the dependent variable (DV) HRQOL;

(d) Studies could be of any quantitative or mixed-method design, except reviews or case studies/series;

(e) There was a language restriction to English, German, Italian, Spanish and Portuguese.

After de-duplication, titles and abstracts were independently reviewed by two reviewers (CR, PK) against the eligibility criteria. Full-texts and results from additional searches were screened by one reviewer only (CR).

Data extraction and analysis

Data on design and outcomes were extracted using a standardised and piloted Excel form. A checklist for prognostic factor studies was used to assess methodological quality [19,20]. The maximum quality score was further stratified into low (<45 points), medium (≥45 to <60), and high quality (≥60) (adapted from Jonge [21]). Discrepancies in scoring and extraction between the

two independent reviewers were resolved by consensus. Overall κ [22] was 0.76. Predictor variables were grouped for data synthesis following the theoretical framework for HRQOL by Wilson & Cleary [23]. Data analysis followed a two-stage approach. First, predictor variables and their outcomes were tabulated and analysed using data synthesis and vote-counting [24]. Vote-counting also provides a more-fine-grained view of all predictors and their associations to subscales as well as total HRQOL scores.

To enable direct comparison of correlations, the HRQOL subscales and total scores were transformed in the same direction with high scores always indicating good HRQOL (multiplying by -1 if necessary). The Pearson *r* was calculated as the effect size metric for the correlations between IVs and HRQOL (either total score or an average of reported domain scores if a total score was not provided). If possible, zero-order correlations were used to estimate effect sizes. Imputation of *r* from other statistical values (beta weights, odds ratios, p values or R^2) was used if necessary [25,26]. In case authors reported that correlations were significant or non-significant an effect size of zero for non-significance and a p value of <0.05 for significance was assigned. This is seen as a conservative approach because the actual p values are likely to have been smaller. Estimation of effect sizes from values other than *r* was necessary in 2/5 of cases, reflecting the heterogeneity in quality of reporting in included studies. Correlation coefficients were transformed into Fisher's z [25] for meta-analysis, back-transformed and plotted in a forest plot. Data from all studies was pooled per independent factor using inverse variance weighting and a random effects model (as more than one population effect size was likely to be estimated due to the heterogeneous nature of multiple myeloma). Weighted effect sizes were considered significant when the 95% confidence interval excluded zero. Effect sizes were categorised into a weak ($r \leq 0.30$), moderate (r=0.30-0.49) and large effect size ($r \geq 0.50$) [27]. Because of necessary independence of effect sizes in meta-analysis [25], each study could only contribute one effect size per independent factor. Heterogeneity could not be assessed due to no pooled overall effect being calculated. Rosenthal's fail-safe N [28] was calculated for estimating publication bias using the formula x=k(average effect size/lowest mean r -1). A criterion effect size of r=0.10 was chosen. Publication bias was not present as the fail-safe N is less than five times the number of existing studies plus ten.

For meta-analysis, the *metafor* package in R 3.0.1 and an SPSS Macro [25] were used. The forest plots were created using Microsoft Excel.

Results

Study characteristics

The database search identified 16,886 articles and other sources yielded 5 further articles (see PRISMA flowchart in Figure 1). Of the 1,259 screened full-texts, the majority (n = 925) was excluded because of failure to report an association or not reporting HRQOL. 54 studies included samples of less than 50% of patients with multiple myeloma. 43 studies were included with 39 presenting enough data for meta-analysis.

Description of included studies

Table 1 presents the study characteristics for HRQOL. The number of articles exceeds the number of studies as some studies were reported in more than one article. 39 studies reporting correlations with HRQOL included 7,391 participants and 7,082 myeloma patients. Of these studies, 21 were longitudinal in nature [29-48]. The pooled mean age across all studies was 60 with a range of 24 to 91. 11 studies used mixed haematological samples with the lowest proportion of myeloma being 53% [49]. The majority of samples were on treatment, receiving stem cell transplantation [5,29-31,45-47,37-39,41,44,49-57], or chemotherapy [33-36,42,43,58-63]

Methodological quality

The detailed quality assessment of all included studies is presented in Online Appendix B. Owing to the high number of cross-sectional studies and conference abstracts, the median quality rating score was low to medium (Median=48.5). Nine studies scored high quality, 24 medium, and ten low quality. Bias was mainly associated with attrition, with little information on those participants lost to follow-up. Prognostic factor measurement was judged poorly because of absence of clear hypotheses. Statistical analysis was poor in some cases (i.e. univariate models in cases where multivariate models would have been more appropriate).

Factors that influence HRQOL

Factors associated with HRQOL were assessed in 34 studies. There was consistency in the choice of measurement tools to measure the outcome (see Table 1). The display of weighted correlation coefficients and their confidence intervals is shown in Figure 2 with values shown in Online Appendix C.

Figure 1 PRISMA flowchart of inclusion of studies

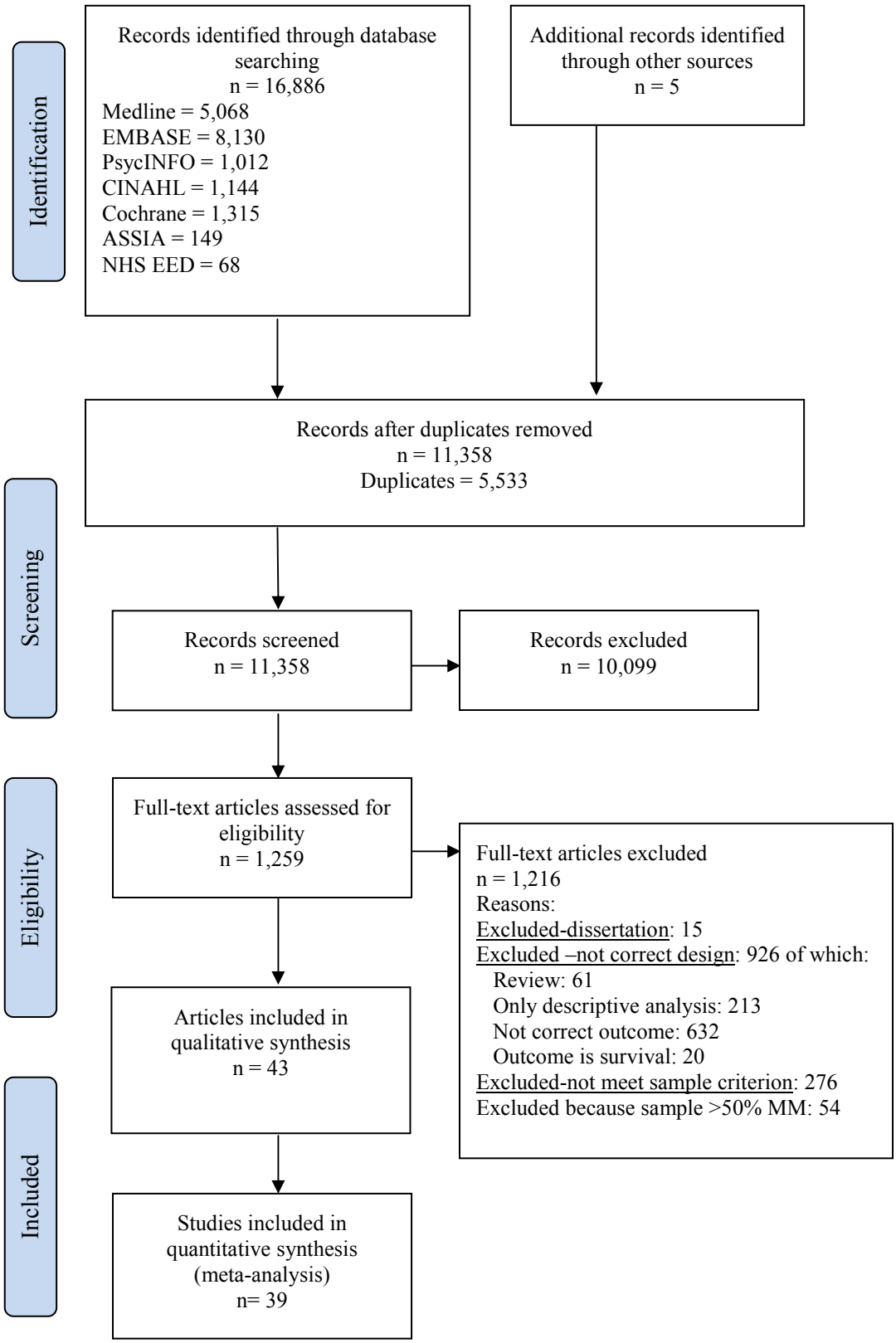


Table 1. Summary of studies reporting associations between independent variables and health-related quality of life

Author, Year Country	Study design and setting	Patient population	% MM	HRQOL outcome	Predictors investigated	Predictors positive
1. Cross-sectional data						
Acaster et al. (2013) [64] United Kingdom	Outpatient ambulatory myeloma patients identified through Myeloma UK	370 MM patients Mean age: 64.6 (SD 8.7) % male: 52%	100%	EORTC QLQ-C30, EORTC QLQ-MY20 EQ5D	Treatment-free interval	Treatment-free interval
Boland et al. (2013) [55] United Kingdom	Outpatient myeloma patients after HSCT and second line treatment	32 MM patients in stable disease Median age: 61 (range 41-71) % male: 53%	100%	EORTC QLQ-C30	BPI, age, sex, years from diagnosis, lines of treatment received, serum interleukin-6, tumour necrosis factor-α	Pain on average, pain interference Serum Interleukin-6, insomnia, appetite loss
Booker et al. (2007) [65] Canada	Not reported (n.r.)	43 MM patients, disease status n.r. Mean age: n.r. % male: n.r.	100%	EORTC QLQ-C30, EORTC QLQ-MY20	Fatigue (FACT-F), haemoglobin, C-reactive protein, albumin	Negative correlations between haemoglobin x CRP, albumin x CRP, QOL x CRP
Booker et al. (2009) [66] Canada	Outpatient ambulatory haematology clinics at a tertiary oncology centre	56 MM patients Mean age: 62 (SD 10.75*) % male: 54%	100%	EORTC QLQ-C30	Fatigue (FACT-F), haemoglobin, C-reactive protein, albumin	C-reactive protein associated with QOL
Coleman et al. (2011) [51] United States	Inpatients, baseline data from trial investigating exercise intervention for tandem PBSCT patients	187 newly diagnosed MM patients Mean age: 56 (SD 10) % male: 58%	100%	FACT-G, Fact-F, FACT-Pain	Age, haemoglobin, fatigue, pain, mood disturbance (POMS), pounds lifted, distance walked, night time sleep, sleep efficiency, ISS stage at diagnosis	POMS total mood disturbance, 6MWD, night time sleep hours and sleep efficiency
Espinoza-Zamora et al. (2015) [62] Mexico	Outpatient myeloma patients recruited for a questionnaire validation study	98 MM patients at different ISS stages Mean age: 58.1 (SD 11.2) % male: 60.6%	100%	EORTC QLQ-C30, EORTC QLQ-MY20	Serum albumin level, serum haemoglobin level, serum beta 2 microglobulin level	All three levels associated with Disease symptoms, haemoglobin
Frick et al. (2004) [49] Germany	Secondary analysis of RCT investigating a psychotherapy programme for patients undergoing high-dose therapy with PBSCT	79 haematological cancer patients (MM, NHL, other) Mean age: n.r. % male: 57%	58.2%	EORTC QLQ-C30 physical functioning, SEIQoL	Karnofsky index, remission status	Positive correlation between Karnofsky index and physical functioning

Frick et al. (2006) [50] Germany	Secondary analysis of RCT investigating a psychotherapy programme for patients undergoing high-dose therapy with PBSCT	60 haematological cancer patients (AML, HL, NHL, others) Mean age: 52.8 (SD 9.6) % male: 55%	53%	EORTC QLQ-C30	Performance status, remission state	Both were related to Global health score, Fatigue and Role function
Jones et al. (2004) [67] Canada	Retrospective survey of outpatients identified through cancer registry	87 MM cancer survivors of all stages Mean age: 64.4 (SD 11.5) % male: 58.6%	100%	FACT-G	BMI, Exercise behaviour during active treatment, exercise during off-treatment periods	BMI correlated with total FACT-G, exercise correlated with FACT subscales, fatigue, anaemia and depression
Jones et al. (2013) [71] United States	Patients undergoing chemotherapy (induction) or SCT	132 MM patients, mainly newly diagnosed Mean age: 62.5 (SD 10) % male: 64.3%	100%	MDASI-MM	ECOG performance status	ECOG Performance status correlated with MDASI-MM subscale scores
Jordan et al. (2010,2013) [60,61] United Kingdom and Germany	Prospective survey of outpatients on- and off-treatment	154 MM patients of all stages Mean age: 66.4 (SD 10) % male: 63%	100%	EORTC QLQ-C30, EORTC QLQ-MY20	Patients' general symptom level and specific myeloma symptoms, adverse effects, demographic variables	Severe bone pain, bone fracture, being severely symptomatic, being on treatment, fatigue, changes in mental status, dizziness, infection, younger age, British patients, treatment longer than 111 days
Leleu et al. (2013) [58], Petrucci et al. (2013) [59] Europe	Observational study with MM patients with relapsed or progressive disease starting 2nd or 3rd line treatment	206 relapsed/progressive MM patients Mean age: 69 % male: 51%	100%	EORTC QLQ-C30, EORTCQLQ-MY20	ECOG performance status, Discontinuation of bortezomib or lenalidomide treatment	Performance status, discontinuation of treatment correlated with total score and subscales
Molassiotis et al. (2011) [68] United Kingdom	Prospective survey of patients from myeloma specialist transplant centre and general district hospitals	132 MM patients of all stages Mean age: 62 (SD 8.8) % male: 61.4%	100%	Cancer Survivors' Unmet Needs, EORTC QLQ-C30, MY20	Unmet partner needs, HADS, EORTC QLQ-C30, MY20, demographic variables	Side effects of treatments, unmet partner needs, partner anxiety, patient anxiety, younger age
Pamuk et al. (2013) [72] Turkey	Descriptive study of myeloma patients, setting n.r.	89 MM patients Mean age: 62.4 (SD 10.1) % male: 61%	100%	EORTC QLQ-C30 global score	EORTC QLQ C-30 and EORTC QLQ MY-20 subscales, HADS	Physical functioning, role functioning, treatment side effects, presence of depression
Pashos et al. (2011, 2013) [73,74] United States	Retrospective and prospective analysis of U.S. cancer registry Connect data	640 MM patients with active, symptomatic disease at different stages Mean age: 60.9 (SD 11.8) % male: 56%	100%	EQ5D, FACT-MM, FACT-G	ECOG and ISS	EQ5D: higher ECOG, ISS stage, FACT-MM: ISS and ECOG with lower physical and functional scores

Paul et al. (2014) [94] United States	Retrospective chart review of newly diagnosed outpatients	453 newly diagnosed MM patients Median age: 67 (range 33-95) % male: 60%	100%	Quality of life rating scale (0-10)	Lower absolute lymphocyte count and serum albumin levels	Both associated with lower QOL scores
Poulos et al. (2001) [69] United States	Prospective survey of MM patients identified from institutional database	206 MM patients of all stages Mean age: 62.9 (SD 10.3) % male: 67%	100%	Quality of Life Scale (Ferrell)	POMS, BPI, demographic and clinical details	Pain interference correlated with POMS, QOL: pain intensity, pain interference, POMS subscales, age, gender, number of comorbidities, time since diagnosis as predictors
Sherman et al. (2003) [54] United States	Baseline evaluation of haematological cancer patients undergoing conditioning before APBSCT	61 haematological cancer patients pre-transplant (MGUS, Amyloidosis, MM) Mean age: 57 (SD 12.3) % male: 64%	85.3%	SF-12	POMS-Fatigue, BPI, HADS, nutritional status, FACIT, haemoglobin, demographic and clinical characteristics	Nutritional risk, pain, fatigue, sexual problems, age, time since diagnosis, haemoglobin, marital status, depression
Sherman et al. (2004, 2005) [52,53] United States	Baseline evaluation of MM patients before undergoing conditioning before APBSCT at large transplant centre	213 MM patients pre-transplant Median age: 59 (range 31-81) % male: 60%	100%	SF-12	Age, gender, education, ethnicity, employment status, tumour stage, months since diagnosis, anxiety, depression, religious coping, strength of religious faith	SF-12 physical composite score predicted by age, education, lower duration of illness, more advanced disease stage, greater emotional distress, negative religious coping
Sherman et al. (2012) [70] United States	Cancer patients treated at a myeloma research and therapy centre	104 cancer patients (85 MM, 16 other haematological cancers, 3 solid tumours) Mean age 56.8 (SD 9.8) % male: 62.5%	81.7%	SF-36 General health item, General distress measured by Taylor Manifest Anxiety Scale	Personal meaning (from Sense of Coherence scale), Relationship cohesion (Dyadic Adjustment Scale), Coping efficacy, Perceived social support, demographic and clinical characteristics	Predictors for general health: gender, allogeneic transplant, social desirability, personal meaning, intrinsic religiosity, social support, emotional control, Predictors for distress: education, social desirability, personal meaning, intrinsic religiosity, social support, emotional control, personal meaning

Tuchman et al. (2015) [95] United States	Cross-sectional study to test the feasibility of exercise testing in MM outpatients	22 MM patients after HSCT in remission Mean age: 60 (SD 7) % male: 73%	100%	FACT-G, FACT-BMT	VO_2peak and peak workload	No significant correlations to physical functioning and FACT-BMT
Van der Poel (2015) [63] Netherlands	Cross-sectional, population-based survey of MM patients in a cancer registry	212 MM patients Mean age: 65.7 (SD 5.8) % male: 57.5%	100%	EORTC-QLQ-C30, EORTC QLQ-MY20	Age, gender, number of comorbidities, time since diagnosis, treatment	Number of comorbidities as only significant correlation with global QOL
2. Longitudinal data						
Anderson et al. (2007) [29] United States Follow-up: 1 month	Observational study, outpatients scheduled to receive autologous PBSCT	100 MM and NHL, disease status not assessed Mean age: 53.6 (SD 9.7) Male %: 60%	66%	MDASI-BMT	Disease type, haemoglobin at baseline, POMS at baseline, FACT-BMT at baseline	Disease type, POMS at baseline and FACT-BMT at baseline
Bartley et al. (2014) [30] United States Follow-up: 6 months	Observational study, patients with haematological malignancies undergoing allo- and auto-SCT at one transplant centre	70 SCT patients (leukemia, MM, HL and NHL patients) Mean age: 57.3 (SD 10.1) % male: 55.7%	57.1%	FACT-G (Social wellbeing) Z-score composite of BPI, PROMIS-Fatigue, SF-36-Sleep, PROMIS-Cognitive abilities	Socio-demographic details, Transplantation type (allograft versus autograft), coping mechanism: Holding back withholding of discussing disease-related thoughts and emotions	Allograft: more health-related symptoms, Holding back correlated with reduced social wellbeing at 3 months, white ethnicity resulted in better social wellbeing
Beguin et al. (2013) [31] Belgium Follow-up: 3 months	Multicentre RCT of darbepoietin-alfa plus intravenous iron after AHSCT	31 (of 96) ASCT patients completed HRQOL information Mean age: n.r. % male: n.r.	61.7%	FACT-Fatigue	Haemoglobin level (<12 g/dl)	Significant correlation between level of fatigue and haemoglobin level
Campagnaro et al. (2008) [32] United States Follow up: 37 months	Observational study, myeloma patients undergoing ASCT with high-dose chemotherapy at large transplant centre	64 MM patients at different stages of disease Mean age: 55.2 (SD* 11) % male: n.r.	100%	MDASI-BMT	MDASI score at baseline, demographic and clinical details, level of lactate dehydrogenase, albumin, haemoglobin, stem cell dose and comorbidities	MDASI-BMT score at nadir was predicted by MDASI Global Symptom severity score at baseline and MDASI Interference scores
Delforge et al. (2009) [33] Belgium Follow-up: n.r.	Observational study of MM patients undergoing bortezomib treatment at several centres	103 relapsed MM patients Median age: 65 % male: 75.7%	100%	EORTC QLQ-C30	Age, gender, line of therapy, laboratory values, responders versus non-responders	Non-responders versus responders showed worse physical, cognitive and emotional functioning, nausea and vomiting, sleep disturbance, and financial

Delforge et al. (2012) [34] Belgium **Follow-up: 9-18 months**	Secondary analysis of RCT data of trial for elderly, transplant ineligible MM patients receiving bortezomib and melphalan versus melphalan alone	649 newly diagnosed MM patients Median age: 71 (range 48-91) % male: 49.3%	100%	EORTC QLQ-C30	Impact of duration of response and complete response, Karnofsky performance status, clinical and treatment details	Global health status predicted by duration of complete response, achieving a response had an impact on global health status, pain and appetite loss
Delforge et al. (2015) [96] Belgium **Follow-up: 18 months**	Secondary analysis of RCT data in newly diagnosed patients receiving lenalidomide plus low-dose dexamethasone vs melphalan, prednisolone an thalidomide	1,623 newly diagnosed MM patients Median: 73 (range 40-92) % male: 52.6%	100%	EORTC QLQ-C30, EORTC QLQ-MY20, EQ5D	Age	Effects of age different in treatment arms
Dimopoulos et al. (2011, 2013) [35,36] Europe Follow-up: 30 months	Secondary analysis of RCT data of melphalan, prednisone and lenalidomide maintenance treatment	459 newly diagnosed elderly MM patients Median age: 71 % male: 49.7 %	100%	EORTC QLQ-C30	Treatment group, age, gender, baseline QOL, treatment response, neutropenia, anaemia	Age, gender, anaemia, baseline global QOL, treatment response
Gulbrandsen et al. (2001) [37] Sweden, Norway, Denmark Follow-up: 36 months	Secondary analysis of RCT data of patients receiving high-dose chemotherapy and ASCT	334 MM patients at different stages Median age: 53.5 % male: 63.2%	100%	Global EORTC QLQ-C30 at 6 months and 12 months	Treatment group and Durie-Salmon stage at baseline	Only treatment group predictor for global QOL at 6 months
Hung et al. (2013) [38] Australia Follow-up: 100 days post-transplant	Autologous PBSCT from an Australian transplant centre	24 haematological cancer patients (MM, HL or NHL, CLL/SLL)	54.2%	EORTC QLQ-C30	Physical activity level (Short form International Physical Activity Level), hand grip strength (objective functioning), fat mass	Change in fat mass, level of physical activity
Jacobs et al. (2007) [39] United States Follow-up: 12 months	Observational psychometric evaluation of patients completed allogeneic or autologous HSCT	101 haematological cancer patients (MM, NHL, HL, ALL, AML and others) Mean age: 52.7 (12.2) % male: 56.4%	63%	FACT-Cognition and EORTC QLQ-C30 cognitive functioning	Demographic and clinical characteristics, CES-D, fatigue, STAI, mental and physical well-being (SF-36), type of transplant	Female gender, depression, fatigue, anxiety, mental and physical well-being correlated with outcomes
Mendoza et al. (2012) [40] United States Follow-up: 2 months	Before-after quasi-experimental study of MM patients treated with kyphoplasty or vertebroplasty for myeloma-related fractures	79 MM patients with myeloma-related fractures Mean age: 60 (SD 9.8) % male: 59.5%	100%	BPI pain severity	ESAS symptom scores, treatment details, demographic variables	Only age significant predictor for pain severity

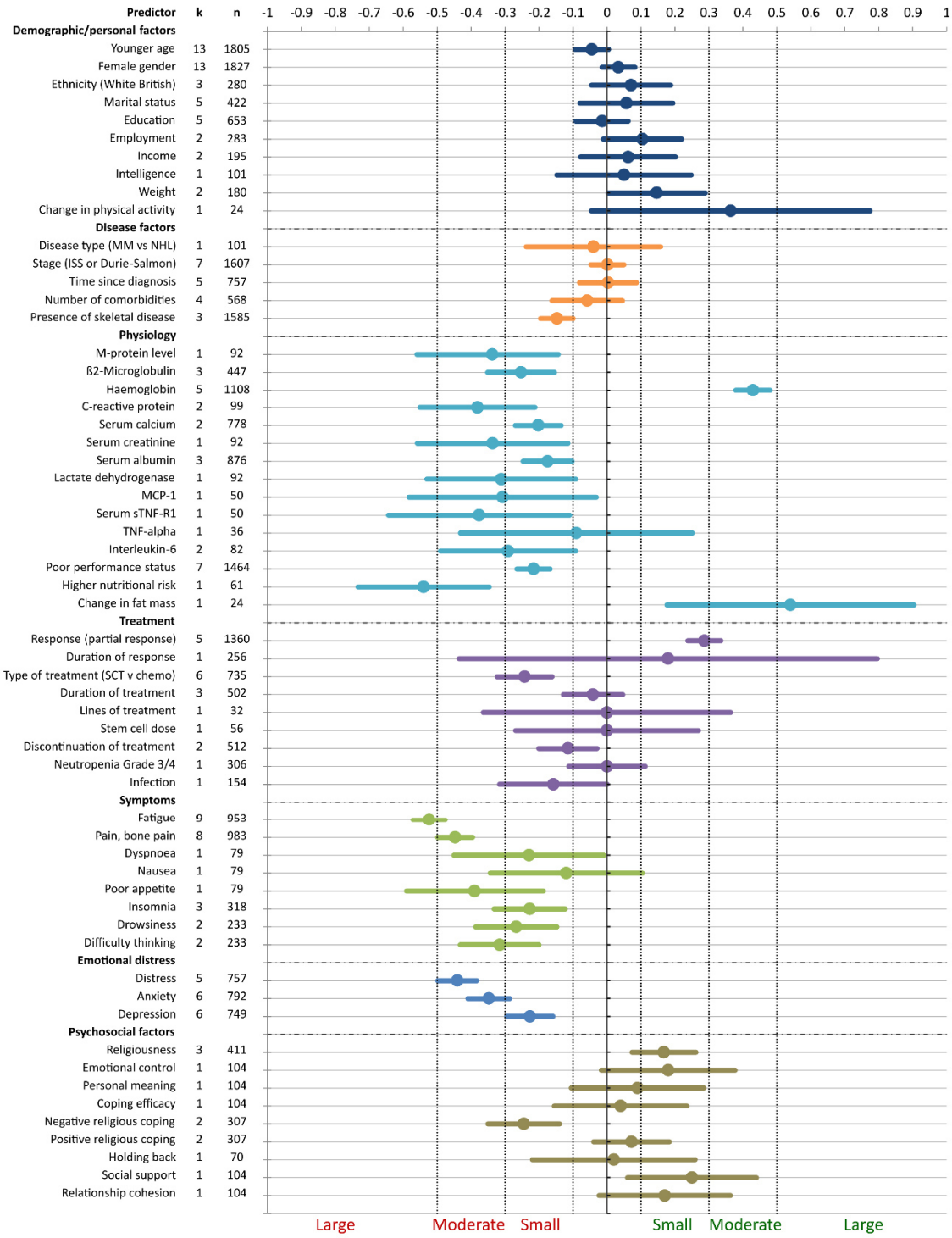
Sherman et al. (2009a,b) [9,41] United States Follow-up: 3 months	Observational study of MM patients pre and post-transplant	94 MM patients undergoing ASCT Mean age: 55.7 (SD 9.2) % male: 61.7%	100%	FACT-G and FACT-BMT, Satisfaction with Life Scale, General distress: Brief Symptom Inventory	Demographic and clinical characteristics, previous HSCT experience, received thalidomide or not, Santa Clara Strength of Religious Faith, Brief RCOPE	Baseline outcome predicted by age, income and negative religious coping; post-transplant outcomes predicted by income, number of transplants, baseline anxiety, negative religious coping, baseline transplant concerns, baseline emotional wellbeing, positive religious coping
Shi et al. (2014) [48] United States Follow-up: 6 months	Longitudinal observational study of outpatients enrolled at 3 months post auto-HSCT	51 MM patients Mean age: n.r. % male: n.r.	100%	EORTC QLQ-C30	Symptom burden	High symptom burden associated with poorer QOL, reduced physical functioning associated with fatigue and bone aches
Strasser-Weipl & Ludwig (2008) [42] Austria Follow-up: 7 years	Secondary analysis of RCT comparing continuous versus intermittent prednisolone in combination with VMCP-IFNalpha2b during induction and IFN2b with or without prednisolone during maintenance	92 newly diagnosed, elderly MM patients, previously untreated Median age: 66 (range 43-84) % male: 55.4%	100%	EORTC QLQ-C30	Demographic and clinical characteristics	In univariate analysis only disease parameters associated with HRQOL, psychosocial HRQOL only weakly related to disease-parameters
Verelst et al. (2011) [43] Netherlands Follow-up: 18 months	Secondary analysis of RCT comparing thalidomide with melphalan + prednisone vs melphalan + prednisone for newly diagnosed MM patients	284 newly diagnosed, symptomatic MM, >65 years Median age: 72 (range 65-84) % male: 56.3%	100%	EORTC QLQ-C30 and EORTC QLQ-MY24	Gender and haemoglobin	No association of haemoglobin, but female gender on nausea/vomiting, appetite loss, specific side effects of myeloma treatment, physical, emotional, social functioning, future perspectives
Wang et al. (2012) [44] United States Follow-up: 6 months	Observational study measuring HRQOL twice a week before ASCT, during and after ASCT	50 MM transplant patients at different stages Mean age: n.r. % male: n.r.	100%	MDASI	Increased sTNF-R1, increased MCP-1, decreased Interleukin-6 receptor (IL-6R)	Increased serum sTNF-R1, increased MCP-1 and decreased IL-6R significantly associated with worsening of symptoms over time
Wang et al. (2015) [97] United States Follow-up: 6 months	Longitudinal observational study of patients 3 months post auto-ASCT	51 MM patients 3 months post auto-ASCT Mean age: 59 % male: 66.7%	100%	MDASI-MM	Beta 2 microglobulin	

Wells et al. (2009) [45] United States Follow-up: 6 months	Observational study of HSCT patients before and after receiving transplant	214 HSCT patients (MM, NHL, HL, AML, CLL, CML, breast cancer and others) Mean age: 51 (SD 12) % male: 52.8%	55.1%	CES-D and STAI-Anxiety	Coping Responses Inventory, Interpersonal Support Evaluation Checklist-Short Form	Depression and anxiety pre-transplant were predicted by female gender and coping mechanisms
Wisløff et al. (2005) [46] Denmark, Norway, Sweden Follow-up: 12 months	Secondary analysis of RCT of high-dose chemotherapy with ASCT	745 newly diagnosed MM patients >60 years Median age: 62 (range 28-87) % male: 59.5%	100%	EORTC QLQ-C30 subscales	Haemoglobin and skeletal disease prior to therapy and at 12 month follow-up, response to therapy	Haemoglobin and response to therapy influenced pain, physical and role functioning and global therapy 12 months post-transplant
Wisløff et al. (2007) [47] Denmark, Norway, Sweden Follow-up: 12 months	Secondary analysis of RCT of high-dose chemotherapy with ASCT	686 newly diagnosed MM patients >60 years Median age: 62 (range 28-87) % male: 59.2%	100%	EORTC QLQ-C30 subscales	Serum calcium, skeletal events, haemoglobin, Serum creatinine, Serum albumin	Serum calcium associated with all QOL subscales, skeletal disease with pain, fatigue, constipation and physical functioning, haemoglobin with fatigue, creatinine with pain and nausea/vomiting, albumin with physical and cognitive functioning

* estimated data, SD imputed as (max – min)/4

Abbreviations: 6MWD: 6 minute walk test; ALL: Acute lymphocytic leukemia; AML: Acute myelogenous leukemia; ASCT: Autologous stem cell transplant; BMI: Body mass index; BMT: Bone Marrow Transplantation; BPI: Brief Pain Inventory ; BSI: Brief Symptom Inventory; CES-D: Centre for Epidemiologic Studies Depression Scale; CRP: C-reactive protein; ECOG: Eastern Cooperative Oncology Group Performance Status; EORTC: European Organization for the Research and Treatment of Cancer; EQ5D: EuroQoL 5D quality of life instrument; ESAS: Edmonton Symptom Assessment Scale; FACT: Functional Assessment of Cancer; HADS: Hospital Anxiety Depression Scale; HL: Hodgkin lymphoma; HRQOL: Health-related quality of life; HSCT: Hematopoietic Stem Cell Transplant; ISS: International Staging System; MCP-1: monocyte chemotactic protein 1; MDASI: M.D. Anderson Inventory; MGUS: monoclonal gammopathy of unknown significance; MM: Multiple myeloma; n.r.: not reported; NHL: Non-Hodgkin lymphoma; PBSCT: Peripheral blood stem cell transplant; POMS: Profile of Mood States; PROMIS: Patient Reported Outcomes Measurement Information System; QOL: Quality of life; RCOPE: Brief Religious Coping Inventory; RCT: Randomized controlled trial; SCT: stem cell transplant; SD: Standard deviation; SEIQoL: Schedule for the Evaluation of Individual Quality of Life; SF-12 and SF-36: Medical Outcomes Study Short Form 12/36; STAI: Spielberger State-Trait Anxiety Inventory; sTNF-R1: serum tumor necrosis factor-R1; U.S.: United States

Figure 2 Pearson weighted correlations between all independent variables investigated in the included studies and the dependent variable HRQOL. Independent variables are grouped into demographic, disease-related, physiological, treatment-related factors, symptoms, emotional distress and psychosocial factors. The outcome HRQOL is scored in a way that a high score indicates better health status/quality of life, thus factors on the left hand side indicate risk factors for poor HRQOL and factors on the right-hand side indicate protective factors.



Legend: ISS: International staging system, MCP-1: monocyte chemotactic protein 1, MM: multiple myeloma, NHL: Non-Hodgkin lymphoma; sTNF-R1: serum tumour necrosis factor-R1, TNF-alpha: tumour necrosis factor alpha, SCT: Stem cell transplant

Few of the demographic, disease-related, treatment-related, physiological, symptoms, emotional distress and psychosocial factors showed moderate to large associations to HRQOL. Demographic factors (age, gender, ethnicity etc.), disease factors (such as stage of disease, time since diagnosis, number of comorbidities) and psychosocial factors had zero to small correlations to HRQOL. For example, gender, ethnicity and weight/BMI were the only three demographic variables that emerged as weakly associated factors to better QOL in the meta-analysis. Female gender showed a low weighted correlation of r = 0.08 (95% CI: 0.03 to 0.13), ethnicity was estimated as r = 0.15 (95% CI: 0.01 to 0.28).

Poorer HRQOL was significantly associated with biochemical/physiological factors and parameters of disease activity such as M-Protein level, $ß_2$-Microglobulin, C-reactive protein, serum creatinine, calcium and albumin and pro-inflammatory factors (IL-6, TNF-α, TNF-R1; r = -0.09 to -0.38). Functional status, assessed using ECOG performance status, the only factor measured in seven studies with 1,464 participants, showed only a weak association to poorer QOL (r = -0.21, 95% CI: -0.27 to -0.16). The strongest negative association (r = -0.54, 95% CI: -0.73 to -0.35) was reported for nutritional risk, defined as change in weight change, change in food intake, difficulty eating and lower functional capacity [51]. Higher haemoglobin was moderately associated with better HRQOL (r = 0.39, 95% CI: 0.33 to 0.44).

No disease-related factor reached moderate to high association. A weak to moderate relationship to HRQOL was found by response to treatment in five studies [31,32,44,46,47] with an *r* of 0.29 (95% CI: 0.24 to 0.34, n=1,360). However, duration of response did not have a significant influence, with a large confidence interval mainly stemming from its differential impact on different domain scores. The only other significant association in this group was found for type of treatment with a negative weak impact on HRQOL (r = -0.19, 95% CI: -0.28 to -0.10, n=453). Receiving thalidomide was negatively associated with role, social and global quality of life (QOL).

By contrast, symptoms had some of the highest correlations to global QOL (single item). The weighted correlation coefficient for fatigue was r = -0.52 (95% CI: -0.57 to -0.47, n=902). The second largest independent factor was pain/bone pain with a moderate association of r = -0.45 (95% CI: -0.50 to -0.39, n=932). Poor appetite and difficulty in thinking/changing mental status had moderate weighted effect sizes. Weighted correlations for drowsiness, insomnia and breathlessness were in the weak range between -0.23 to -0.27 (see Figure 2). Effects were mainly observed on physical, social and global QOL.

All three emotional factors, global distress, anxiety and depression were moderately correlated (ranging from r = -0.23 (95% CI: -0.30 to -0.16; n=749) with depression to r = -0.44 (95% CI: -0.50 to -0.38, n=757) with global distress). Various psychosocial factors, ranging from personality

factors (religiousness, emotional control), cognitive appraisal of illness, coping (in the form of coping efficacy and positive/negative religious coping), and interpersonal factors (perceived social support, relationship cohesion) showed association in the non-significant to weak range.

Discussion

This is the first systematic review in haematology/oncology that used meta-analytical procedures to understand the relative impact of factors related to HRQOL in myeloma. Our review expands on the available evidence [9–14] for the importance of factors impacting on outcomes of HRQOL in multiple myeloma in three ways. (1) More factors, especially relating to disease activity have been included; (2) by computing effect sizes a direct comparison between factors allows an interpretation of their respective importance further than possible in a narrative synthesis; and (3) bias due to overlap between HRQOL and symptom scales present in the vote-counting approach was avoided by only considering correlations to global QOL items. The reported heterogeneity around traditionally examined risk factors such as demographic variables (age, gender, ethnicity, and educational background), disease or psychosocial factors [9–12] could therefore be resolved.

Our analysis indicates that nutritional risk (in the form of weight loss, loss of lean muscle mass or reduced physical activity), fatigue and pain are the most important factors leading to poor HRQOL. Overall, these three indicators are more important than traditionally examined demographic risk factors (age, educational background) or stage of disease. A growing body of evidence supports the extent of fatigue in terms of its high prevalence and its impact on quality of life. Both fatigue and weight loss/anorexia-cachexia syndrome have been linked to shorter survival in the advanced, palliative stages of disease [75-77]. Thus, both variables could act as risk factors for low well-being and shorter survival in myeloma. Research in cancer patients points towards inflammatory processes (cytokines), anemia and metabolic status contributing to cancer-related fatigue alongside behavioural and well-being factors [76,78], which might explain the high correlations. Therefore, a focus on improving quality of life through addressing issues of fatigue and nutritional risk through counselling and behavioural interventions (like physical exercise) [79,80] could benefit those with particularly low quality of life in multiple myeloma.

A small risk effect of ethnicity was shown for the Black African or Caribbean population in the UK having worse HRQOL. This finding supports the evidence of higher psychological morbidity and lower quality of life associated with an ethnic minority background from the United States [81].

Traditional endpoints of response to treatment were only weakly to moderately associated with HRQOL with correlation coefficients much smaller than those for symptoms. Overall, it is not well understood how response and duration of response relate to toxicity profiles of therapy and

impact on HRQOL [82,83]. We found that response to treatment and duration of response are not good proxy outcomes for HRQOL. Evaluation of patients in a clinical setting that only focuses on these criteria [84] will miss the patient-centred perspective and cannot reflect the impact that the disease and/or treatment have on the patient and his or her well-being. Outcomes like time to progression, progression-free survival, response and duration of response are currently the advocated primary outcome for phase III trials [82], a perspective that disregards the impact these treatments might have on the patient's quality of life [85]. It has also prohibited the exploration of the linkage between HRQOL and survival, an avenue which showed prognostic significance in solid tumours [77,89,90]. This finding shows the need to assess HRQOL using patient-reported outcome measures in addition to biochemical monitoring of myeloma in a clinical setting.

Clinically, the findings from the meta-analysis also imply that stage of disease, time since diagnosis and number of comorbidities [84] do not serve as good proxies for HRQOL. However, surveillance of biochemical parameters on their own (haemoglobin, calcium elevation, high serum creatinine, presence of bone disease and lactate dehydrogenase), prognostic factors for relapse and overall survival in myeloma [86] do show moderate correlations. The disconcordance between importance of biochemical and disease parameters is insofar surprising as staging systems for myeloma rely on the biochemical evaluation of disease [84]. Rather than the combined score, surveillance of these biochemical parameters may prompt clinicians to indicate the need for more thorough screening and assessment of quality of life. Recent electronic systems allow monitoring of HRQOL and adverse events for haematological patients receiving stem cell transplants or chemotherapy [15,16]. Screening and monitoring of HRQOL and symptoms would enable targeting supportive care services towards those in need and might help better symptom management, an avenue that warrants further exploration.

Limitations

The main limitation of this review concerns the inclusion of cross-sectional studies in a review of prognostic factors, which ideally relies on longitudinal research with a clear time-event pattern [87]. Hence, the results of the meta-analysis show the strength of association but not prognostication. However, exclusion of cross-sectional studies would have limited the generalisability of findings (see Appendix D). To counteract bias we refrained from calculating an overall pooled estimate. The review group opted for inclusion of studies that had at least 50% myeloma patients. 53 more studies had myeloma patients in the sample, but the majority less than 5%. Also, a sensitivity analysis which excluded those studies with less than 100% myeloma did not alter the results of the meta-analysis. However, inclusion of mixed haematological samples resulted in associations between some factors and QOL being reported that might be important for a smaller part of myeloma patients, such as allografting [30].

The heterogeneity in the assessment of independent variables and in the outcome (presentation of associations to subscales or overall QOL) limits the interpretation of findings. For the pooling of

results, comparability of QOL measures was assumed [91]. This is debatable as health status measures might be different to measures of subjective well-being [88]. However, the effect sizes reported are robust and do not reflect the overlap of symptoms and quality of life outcomes, as only correlations between symptoms and overall quality of life (single item scale) were considered in the meta-analysis.

The small number of studies per independent factor also counteracted the benefit of the meta-analytic approach that can provide estimates of effect sizes not limited by issues of small sample size and power [25,92]. A power calculation revealed that in order to detect a weak to moderate effect of r = 0.20-0.30, a study with a significance level of 95% and a power of 80% would need 119 participants. The smallest sample size in this review was 24 [38]. This might be the reason for some of the large confidence intervals and small correlations seen. Two fifth of correlation coefficients were imputed from other statistical information. Some authors argue against imputation of effect sizes from this data [91-93]. However, without imputation many factors could not have been considered. A conservative approach was followed throughout, and resulting correlation coefficients are most likely under-estimates of the real effect size. Lastly, bias might have been introduced by the independent second reviewer only reviewing the titles and abstract screening and quality assessment, but not the full-text screening and all of the data extraction.

Conclusions

In summary, nutritional risk, fatigue, pain and low haemoglobin are the most important risk factors for poor HRQOL in multiple myeloma. This meta-analysis highlights the need for good symptom management and patient-centred assessment alongside biochemical surveillance of disease progression to improve patient-monitoring, treatment and care. Early detection of those at risk for developing poor HRQOL should therefore consider symptoms as well as biochemical factors and cannot focus on response to treatment and assessment of paraprotein alone.

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Conflict of interest statement

The authors declare no competing interests.

Appendix A. Search strategies

Appendix B. Assessment of methodological quality of included studies

Appendix C. Results of meta-analyses for health-related quality of life

Appendix D. Forest plot of weighted correlation coefficients for longitudinal studies only

Contribution of authors: IJH led the application for funding in collaboration with SAS, RJS and PME, who designed the overall study. CR contributed to the conception, study design, data collection, analysis and interpretation of data and co-ordination of this meta-analysis and review. PMK contributed to the acquisition and analysis of data. RJS, WG, PME, SAS and IJH contributed to the conception, design and conduct of the study with IJH acting as senior researcher overseeing the project. CR drafted the manuscript. All other authors provided comments and critical revisions. The final manuscript was approved by all authors prior to submission. CR and IJH are co-guarantors.

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Appendix A

Sample of full search strategies (used in Ovid Medline) (This search strategy was adapted to all the databases used in this systematic review)

The search filter for myeloma was adapted from the Cochrane Haematological Malignancies group.[1] Two search filters were combined and adapted for identification of HRQOL studies.[2,3]

Search Block 1: Multiple myeloma		**Search block 2: Quality of life**
exp Multiple Myeloma/ OR exp Plasmacytoma/ OR exp Leukemia, Plasma Cell/ OR exp Lymphoma, Non-Hodgkin/ OR exp Haematopoietic Stem Cell Transplantation/ OR exp Stem Cell Transplantation/ OR exp Bone Marrow Transplantation/ OR myelom$.mp. OR plasm?cytom$.mp. OR plasmozytom$.mp. OR plasm$ cell myelom$.mp. OR myelomatosis.mp. OR (plasm$ adj3 neoplas$).mp. OR kahler$.mp. OR non-hodgkin$.mp. OR nonhodgkin$.mp. OR (non adj2 hodgkin$).mp. OR NHL.ti. OR NHL.ab. OR autolog$.mp. OR auto-transplant$.mp. OR autotransplant$.mp.	AND	Quality of Life/ OR quality of life.mp. OR Value of Life/ OR Health Status/ OR Health Status Indicators/ OR health status.mp. OR Quality-Adjusted Life Years/ OR quality adjusted life.ti,ab. OR (qaly$ or qald$ or qale$).mp. OR qtime$.ti,ab. OR Treatment Outcome/ OR disability adjusted life.ti,ab. OR daly$.tw. OR Outcome Assessment (Health Care)/ OR (HR-PRO or HRPRO or HRQL or HRQoL or QL or QoL).ti,ab. OR (health index* or health indices or health profile*).ti,ab. OR health utili$.tw. OR ((patient or self or carer or proxy) adj (appraisal* or appraised or report or reported or reporting or rated or rating* or based or assessed or assessment*)).ti,ab. OR ((disability or function or functional or functions or subjective or utility or utilities or wellbeing or well being) adj2 (index or indices or instrument or instruments or measure or measures or questionnaire* or profile or profiles or scale or scales or score or scores or status or survey or surveys)).ti,ab. OR quality of wellbeing.tw. quality of well being.tw. OR qwb.tw. OR VAS.tw. OR Personal Satisfaction/ OR satisfaction.mp.

Appendix B

Table: Assessment of methodological quality of included studies[4]

Study	Study partici-pation	Study attrition	Measurement of prognos-tic factor	Measurement of outcomes	Statistical analysis	Total quality	Quality cate-gorised
Acaster (2013)	10·5	3	10	15	11·3	49·8	+/-
Anderson (2007)	13·5	6	11·3	12·5	5·6	48·9	+/-
Bartley (2014)	10·5	9	12·5	15	11·3	58·3	+/-
Beguin (2013)	15	10·5	12·5	15	9·4	62.4	+
Boland (2013)	9	0	12·5	15	3·8	40·3	—
Booker (2007)	12	3	11·3	12·5	9·4	48·2	+/-
Booker (2009)	10.5	3	11.3	12.5	9.4	46.8	+/-
Campagnaro (2008)	13·5	7·5	10	12·5	7·5	51	+/-
Coleman (2011)	12	0	12·5	15	7·5	47	+/-
Delforge (2009)	10·5	0	4	10	7·5	23	—
Delforge (2012)	13·5	6	12·5	15	13·3	60·3	+
Delforge (2015)	13·5	6	12·5	15	13·3	60·3	+
Dimopoulos (2014)	13·5	9	13·8	15	15	66·3	+
Espinoza-Zamora (2015)	10.5	6	10	15	5.6	47.1	+/-
Frick (2004, 2006)	13·5	3	15	12·5	9·4	53·4	+/-
Gulbrandsen (2001)	10·5	3	11·3	12·5	11·3	48·5	+/-
Hung (2013)	12	3	10	15	5·6	45·6	+/-
Jacobs (2007)	12	9	10	15	9·4	55·4	+/-
Jones (2004)	13·5	1·5	7·5	12·5	15	50	+/-
Jones (2013)	9	3	9·3	15	7·5	43·8	—
Jordan (2010, 2013)	12	1·5	10	15	15	56	+
Leleu (2013)	3	0	7·5	10	1·9	22·4	—
Mendoza (2012)	9	0	11·3	15	15	50·3	+/-
Molassiotis (2011)	15	0	11·3	10	13·1	49·4	+/-
Pamuk et (2013)	1·5	0	2·5	7·5	3·8	15·3	—
Pashos (2011, 2013)	7·5	0	6·3	7·5	3·8	25	—
Paul (2015)	1·5	0	2·5	7·5	3·8	15·3	—
Poulos (2001)	13·5	0	10	10	13·1	46·6	+/-
Sherman (2003)	10·5	0	12·5	12·5	11·3	46·8	+/-
Sherman (2004, 05)	15	10·5	12·5	12·5	13·1	63·6	+
Sherman (2009a,b)	15	10·5	12·5	15	13·1	66·1	+
Sherman (2012)	15	0	12·5	12·5	15	55	+/-
Shi et al. (2015)	1·5	0	2·5	7·5	3·8	15·3	—
Strasser (2008)	12	0	10	10	15	47	+/-
Tuchman (2015)	10·5	0	12·5	12·5	11·3	46·8	+/-
van der Poel (2015)	10·5	0	12·5	12·5	11·3	46·8	+/-
Verelst (2011)	12	0	11·3	10	15	48·3	+/-
Wang (2012)	4·5	0	10	15	1·9	31·4	—
Wells (2009)	15	10·5	8·8	7·5	15	56·8	+/-
Wisløff (2005, 2007)	10·5	0	10	10	15	45·5	+/-

* Quality: +: high; +/-: moderate; —: low[47]

Appendix C

Table: Results of meta-analysis for health-related quality of life

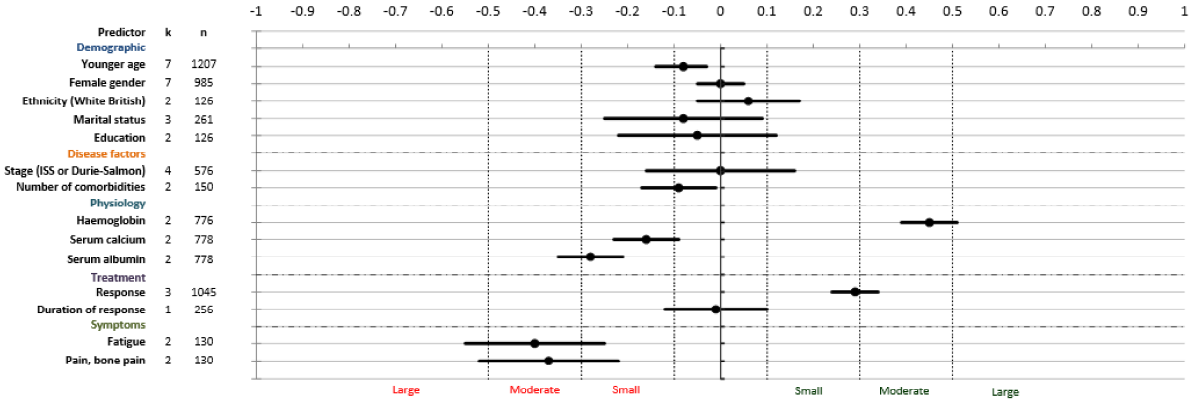
Variable	*k*	*N*	*Effect size*	*Lower 95% CI*	*Upper 95% CI*	*Fail-safe n*
Demographics						
Younger age	12	1593	-0·04	-0·09	0·01	7
Female gender	12	1615	0·03	0·02	0·08	2
Ethnicity	3	280	0·07	-0·04	0·19	8
Marital status	5	422	0·06	-0·08	0·19	3
Education	5	653	-0·01	-0·09	0·06	3
Employment	2	283	0·10	-0·01	0·22	1
Income	2	195	0·06	-0·08	0·20	1
Intelligence	1	101	0·05	-0·15	0·25	1
Weight,	2	180	0·15	0·00	0·29	1
Change in physical activity	1	24	0·36	-0·15	0·25	1
Disease factors						
Disease type	1	101	-0·04	-0·24	0·16	1
Stage	7	1607	0·00	-0·05	0·05	7
Time since diagnosis	4	545	0·00	-0·08	0·09	3
Comorbidity	3	356	-0·06	-0·16	0·05	1
Skeletal disease/bone fractures	3	1585	-0·15	-0·20	-0·10	2
Physiological factors						
M-protein level	1	92	-0·34	-0·56	-0·14	2
ß2-Microglobulin	2	349	-0·25	-0·35	-0·15	3
Hemoglobin	4	1010	0·39	0·33	0·44	9
C-reactive protein	2	99	-0·38	-0·55	-0·21	6
Serum calcium	2	778	-0·20	-0·27	-0·13	2
Serum creatinine	1	92	-0·34	-0·56	-0·12	2
Serum albumin	2	778	-0·18	-0·25	-0·10	4
Lactate dehydrogenase	1	92	-0·31	-0·53	-0·09	2
MCP-1	1	50	-0·31	-0·58	-0·03	2
serum Tumor necrosis factor-R1	1	50	-0·38	-0·64	-0·11	3
Tumor necrosis factor-alpha	1	36	-0·09	-0·43	0·25	1
Interleukin 6	2	82	-0·29	-0·49	-0·09	3
Performance status	7	1464	-0·21	-0·27	-0·16	6
Nutritional risk	1	61	-0·54	-0·73	-0·35	4
Change in fat mass	1	24	0·54	-0·18	0·90	1
Treatment factors						
Response	5	1360	0·29	0·24	0·34	10
Duration of response	1	256	0·18	-0·44	0·80	1
Type of treatment	5	523	-0·24	-0·32	-0·16	4
Duration of treatment	3	502	-0·04	-0·13	0·05	2
Lines of treatment	1	32	0·00	-0·36	0·37	1
Stem cell dose	1	56	0·00	-0·27	0·27	1
Discontinuation of treatment	2	512	-0·12	-0·20	-0·03	1
Neutropenia grade 3 or 4	1	306	0·00	-0·11	0·11	1

Variable	*k*	*N*	*Effect size*	*Lower 95% CI*	*Upper 95% CI*	*Fail-safe n*
Infection	1	154	-0·16	-0·32	-0·00	1
Symptoms						
Fatigue	8	902	-0·52	-0·57	-0·47	29
Pain/bone pain	7	932	-0·45	-0·50	-0·39	20
Dyspnoea	1	79	-0·23	-0·45	-0·01	1
Nausea	1	79	-0·12	-0·34	0·10	0
Poor appetite	1	79	-0·39	-0·59	-0·19	3
Insomnia	3	318	-0·23	-0·33	-0·12	4
Drowsiness	2	233	-0·27	-0·39	-0·15	3
Difficulty thinking	2	233	-0·32	-0·43	-0·20	4
Emotional distress						
Distress	5	757	-0·44	-0·50	-0·38	17
Anxiety	6	792	-0·35	-0·41	-0·29	15
Depression	6	749	-0·23	-0·30	-0·16	8
Psychosocial factors						
Religiousness	3	411	0·17	0·07	0·26	2
Emotional control	1	104	0·18	-0·02	0·38	1
Personal meaning	1	104	0·09	-0·11	0·29	0
Coping efficacy	1	104	0·04	-0·16	0·24	1
Negative religious coping	2	307	-0·25	-0·35	-0·14	3
Positive religious coping	2	307	0·07	-0·04	0·18	1
Holding back	1	7	0·02	-0·22	0·26	1
Social support	1	104	0·25	0·06	0·44	2
Relationship cohesion	1	104	0·17	-0·02	0·36	1

Abbreviations: k=Number of studies, N = Number of participants per studies included in that factor

Appendix D

Forest plot of Pearson weighted correlations between all independent variables and the dependent HRQOL for longitudinal studies only.



The outcome HRQOL is scored in a way that a high score indicates better health status/quality of life, thus factors on the left hand side indicate risk factors for poor HRQOL and factors on the right-hand side indicate protective factors.

2.2.3 Longitudinal assessment of quality of life in clinical practice

The importance of measuring not only the objective effects of cancer and its treatment but focusing on the patients and their perceptions of the illness, its effects and the effects of treatment have formed a central part of patient-centred care in the last 30 years (2,387). Almost thirty years ago, the term patient-reported outcome (PRO) was introduced by Paul Ellwood as a new technology of patient experience to transform medical care (388). Improvements in how patients feel and function was aimed to be seen as legitimate as clinical benefits and survival (389). PRO is an umbrella term to describe "any report of the status of a patient's health condition that comes directly from the patient" (287, p.2). PROs include measurements that require patient input and comprise multidimensional QOL measures to focused, single-domain measures of symptom severity or impact (390). As such, PROs belong to the larger field of outcomes research, a scientific field that seeks to understand the final endpoints that matter to decision makers in health – patients, providers, and governments (362). These outcomes have been defined as the "five Ds" (391) – death, disease, disability, discomfort, and dissatisfaction. The latter three can only be evaluated from the patient's perspective. However, a distinction is made between PROs that cover changes in the patient's health status, and patient experience measures that cover satisfaction (392-394).

Since the U.S. Food and Drug Agency adopted PROs in their guidance, HRQOL outcome measures have become an integral part of cancer clinical trials (287). The same trend can be seen in Europe where the European Organisation for Research and Treatment of Cancer group (EORTC) formed in 1984 and promoted their use, a mission that has been helped by developing the EORTC family of questionnaires that are among the most widely used QOL measures in clinical trials (1). Recent pooling of studies has enabled the development of item banks for the EORTC (395-398). Also, guidance on the use of HRQOL measures in clinical practice is available from the International Society for Quality of Life Research (ISOQOL) and the EORTC (399-401).

Apart from using PROs in treatment effectiveness research, there has also been a push to use PROs in routine clinical practice. In medicine, the traditional way of assessing change and tracking the status of individual patients over time has been to focus on laboratory data and clinical tests (316). Whilst this information is useful, it does not give a complete picture and may miss important areas of unmet need, particularly in chronic and progressive disease (402). Several organisation, among them the FDA, clinical oncological societies and the ISOQOL have issued statements and guidelines establishing the importance of PROs as outcomes in clinical research and to guide decision making (287,403,404). This is hypothesised to help timely, patient-centred and evidence-based care and to help individual treatment planning and decision making as well as

quality improvement (316). Especially in the UK, routine use of PROs has been helped by the initiative of the National Health Service (NHS) to routinely collect PROs, first in a few elective surgery disciplines but now expanded to many other conditions such as breast cancer (405,406). The USA have a nationally funded system of Patient-Reported Outcomes Measurement Information (PROMIS) that has provided PROs and QOL measures to the public via web-based applications (407-410).

The rationale behind using these measures in routine clinical practice is that they are envisaged to help symptom identification and thereby patient satisfaction by improving patient-clinician communication (411). It improves the accuracy with which symptoms are assessed and can potentially safe time during clinic visits (412). Profound differences between patient-reported and clinician-assessed symptoms have been reported, calling into question the validity and reliability of clinician reports that are biased by underreporting and under-detection of symptoms (412-414). Use of HRQOL information can also guide clinical decision making (415). Twelve systematic reviews have tried to establish the effectiveness and impact that routine collection of PROs has on patients, providers and health organisations (see Table 3) (37,416-426). They conclude that there is mixed evidence for the impact of PROs for improving patient management and that heterogeneous results mainly stem from methodological problems and a lack of clarity around the intended use of PROs in clinical practice as well as the lack of theory behind their use and their implementation.

Table 3: An overview of twelve systematic reviews of effectiveness of routine collection of PRO data

First author, year	Aim	Time span	Number of included studies	Major conclusions
Etkind et al. (2015) (37)	To understand by which methods PROs are captured, transferred and their results fed back in palliative care populations and to determine the effect of PRO feedback on processes and outcomes of care.	1985-2013	13	Scarce evidence for palliative care, most evidence from outpatient oncological populations. Strong evidence for the impact of PRO feedback on processes of care, but no large effects on outcomes of care (no effect on QOL and symptom burden, small to moderate effect on caregiver distress and patient distress/emotional burden).
Howell et al. (2015) (416)	The review focused on the identification of PROs used in routine cancer clinical practice, the impact on patient, provider, and systems outcomes, and the implementation factors influencing uptake.	2003-2013	30	Mixed impact on patient outcomes: no significant results on patient satisfaction, positive to mixed results on perceived quality of care. Processes of care: good evidence for better patient-clinician communication, clinical decision making, symptom monitoring (but not improvement).

First author, year	Aim	Time span	Number of included studies	Major conclusions
Kotronoulas et al. (2014) (417)	The review examined whether inclusion of PROs in routine clinical cancer practice improves patient outcomes, processes of care, and health service outcomes during active anticancer treatment.	1950-2012	24	Patient outcomes: effect sizes range from 0.01 to 0.75 for reduction of symptom burden; no significant effect for QOL, d=0.15 to 0.42 for reduction of psychological distress, small to moderate effect for reduction of supportive care needs. Processes: Better patient-clinician communication, decision making, healthcare professionals' awareness of outcomes, but no effect on higher referral rates to psychosocial care.
Chen et al. (2013) (418)	What are the impacts of composite measures of PROs collected on cancer patients during treatment with regards to: a) provider behaviour for improving care delivered, b) organisational change within health care settings, c) improving clinical outcomes for patients, d) improving patient experience of care.	2000-2011	27	Strong evidence for well-implemented PROs improving patient-provider communication and patient satisfaction, weak or non-existent evidence base for changes to patient management and improving health outcomes, changes to patient behaviour, and quality improvement in organisation.
Boyce et al. (2013) (426)	To assess the impact of providing healthcare professionals with feedback on patient-reported outcome measures (PROMs).	2012	17	Feedback at group-level: no statistical difference; only one study provided patient-level feedback and found an overall significant effect. Six studies found significant effects for subgroups of patients, PROs used as management tools and not for screening.
Luckett et al. (2009) (419)	To identify future strategies for interventions to impact patient outcomes and trial to identify treatment effects.	2006-2008	6	Cluster RCTs are needed. More specific PROs should be used, improving the interpretability of feedback for both staff and patients is important.
Valderas et al. (2008) (420)	To summarise the best evidence regarding the impact of providing patient reported outcomes information to health care professionals in daily clinical practice.	1978-2007	28	Methodological concerns limit the strength of evidence. There is great heterogeneity of impact, context and interventions need to be clearly defined.
Marshall, Haywood & Fitzpatrick (2006) (421)	To synthesise the evidence for using publically reported performance data to improve quality.	1976-2004	40	Studies do not evaluate PROs as a means to facilitate patient care. The pattern of results suggests a general lack of clarity in the field, especially regarding appropriate goals for PROs and the mechanisms by which they might achieve them.

First author, year	Aim	Time span	Number of included studies	Major conclusions
Gilbody, House & Sheldon (2001,2002) (422,423)	To assess the best available evidence on the value of routine HRQoL and needs assessment in: (1) improving the psychological care and outcome of people being managed in non-psychiatric settings and, (2) improving the quality of care and outcome of those with common mental disorders.	1966-2000	9	Impact on processes of care: increased recognition of psychological symptoms, but no impact on patient management (increased referrals) or outcomes.
Espallargues, Valderas & Alonso (2000) (424)	To assess the impact on the process and the outcomes of care of feeding back information on perceived health status to health care professionals in clinical practice.	1982-1999	21	Impact on processes of care (service utilisation, diagnosis, treatment and patient satisfaction), but no influence on patient's functional or health status.
Greenhalgh et al. (1999) (425)	To review the evidence for the effectiveness of using patient-based measures of health in routine practice in improving the process and outcomes of individual patient care.	1987-1999	13	Little evidence that use of PROs substantially changes patient management or improves patient outcomes. Implementation strategies need to be guided by theories of individual and organisational change to address barriers.

To remedy this shortcoming, Greenhalgh et al. (2005) (427) have since applied a theory-driven approach for the use of HRQOL measures in clinical practice. They hypothesised mechanisms and paths through which the provision of information on QOL could lead to improved patient satisfaction and health outcomes for patients (38,427). One large area of concern that remains under-explored in studies was identified to be the area of feedback. Feedback was found to be given on a single occasion only with the recipient being the oncologist or doctor but not other health professionals like nurses, social workers, or the patients themselves. This was seen to be contrary to the reality of care in which a range of clinicians was involved (428), decision making occurred as a shared process between several clinicians and over several encounters with the patient (429). From this theoretical model the research group developed the following taxonomy of how PROs could be used in clinical practice (see Table 4).

If PRO information is discussed between clinicians and patients individually, depending on who provided the data (the patients themselves or data was aggregated from a group of patients), this information can be used to directly influence assessment and care of the individual patient in the form of screening or monitoring. Group-level data is applied to the individual patient when providing decision aids (430). Discussion of data from the individual patient by a group of

clinicians is used for multi-disciplinary team meetings. At the national level, such aggregated data is used for population monitoring. Greenhalgh's taxonomy (38) was built on the older conception by Sutherland & Till (1993) (431), who proposed three levels of decision making within the healthcare system at which PRO use could aid clinical utility and bring benefit: (a) micro-level decision making, concerned with decision making involving patients and health care professionals; (b) meso-level decision making, concerned with decisions about approaches to health care for a group of patients within regions; and (c) macro-level decision making, concerned with decisions for population benefit by policy makers and society.

Table 4: Taxonomy of applications of PROs in clinical practice (taken from (38))

	Level of aggregation of PRO data		
		Individual	Group
Used at the clinician-patient interface	Yes	Screening Monitoring Promoting patient-centred care	Decision aids
	No	Facilitating communication within MDTs	Population monitoring Assessing quality of care

Some of the areas shown in the taxonomy have been more widely researched than others. The bulk of the evidence currently exists for screening (421-424), promoting patient-centred care (411,432), and decision aids (430,433); and only some studies exploring the capacity of PROs to facilitate communication within multi-disciplinary team meetings (434-437) and population monitoring (405,437-439). PROs have been adopted as quality improvement tools in the UK (405,440), America (441), Australia (442-444), Sweden (441) and other countries.

Assessing the performance and quality of services is another role for aggregated PROs at the population level (440). This approach has been particularly followed in the setting of rehabilitation and long-term neurological conditions, with national databases/registries mandating input of PROs from each service to arrive at a national comparison of the quality of services and establishing benchmarks for the quality of care (442,443,445-447). This application of PROs is very much in line with Donabedian's definition of outcomes within the quality of care framework (448). Outcome is defined as a change in the patient's health status that can be attributed to preceding health care (448). This information allows an assessment of effectiveness and cost-effectiveness of services, and – in the case of existing casemix classification variables (449) – can guide a direct comparison between services based on patient complexity and patient need. HRQOL in this context is perceived as the ultimate outcome of care. The quality of care is

hypothesised to have a direct influence on HRQOL, but this relationship might be mediated by patient characteristics and patient preferences (431,448). Consequently, evidence for the effectiveness of PROs in improving service quality is weak (37,416-426). It can be expected that more applications of PROs at the national level will help to address these challenges. According to Donaldson (2008) (450), PROs are now a technology that has come of age, with translation into the healthcare system (use in clinical practice, post-market surveillance, cost-effectiveness) meaning PROs may soon become the standard of care.

The area of longitudinal monitoring is particularly under-explored. Only few studies have used this application. There is some evidence from psychotherapy, in which one study has shown the effectiveness of longitudinal monitoring of PROs for predicting treatment failure or poor response to therapy (451,452). However, with the advent of new technologies and the more widespread use of the internet, electronic patient-monitoring is an avenue that should be explored more widely. The availability of user-friendly, electronic platforms or tablet computers has made it possible to standardise methods of PRO monitoring and using the data in real time. These systems also allow that alerts are sent to the clinic once scores indicate clinically relevant problems in certain areas. It also provides the opportunity to provide patients electronically with educational material tailored towards their needs (453). An overview of current systems using this approach in oncology and palliative care is given in Table 5.

Although these new initiatives certainly facilitate the integration of PROs in clinical practice and address how monitoring could be established in a feasible way, gaps remain unaddressed. In fact, as can be seen in Table 5, most often results from QOL questionnaires are not given to the patient directly but remain with the clinician. Furthermore, these systems are held within clinics. In the United Kingdom a study has begun to prospectively monitor the HRQOL changes in cancer survivors. This study uses display of HRQOL information directly to the patient (470,471). This area needs further exploration. Specifically, it is not clear

- what modifications to existing questionnaires are needed or which questions perform well in longitudinal monitoring,
- which questions have sufficient discriminatory function to distinguish between subgroups of patients,
- which questions have enough diagnostic power to indicate when a clinically important threshold is reached to send out an alert to the clinic for the patient to be seen,
- which questions have high predictive validity and are indicative of subsequent poor outcomes (like high health care utilisation, cost or survival),

- how results should best be fed back to clinicians and patients and which interpretation aids might be useful.

Table 5: Overview of current initiatives using electronic patient-monitoring to support clinical oncological care (based on (453) and (454)).

System	University	Population	Survey mode and content	Information given to
Patient viewpoint (455,456)	Johns Hopkins University	Cancer treatment and survivorship	Web-based reporting from home; information to clinician and patient	Clinician and patient
Patient care monitor and ePRO system (457-459)	Duke Comprehensive Cancer Center	Treatment and survivorship	Touch-screen computers in clinic; information to clinician	Clinician and patient
Monitoring adverse events and GVHD (460-463)	Fred Hutchinson Cancer Centre	Patients undergoing HSCT	Web-based reporting from home; information to clinician	Clinician only
Electronic Self Reporting Assessment (ESRA/STAR) (41-44,464)	Harvard Medical School	Oncology and haematology patients	Touch-screen computers in clinic; information to clinician	Clinician only
TellUs (465)	Hospice services in the UK	Palliative care	Web-based reporting from home; information to providers	Clinician only
Wireless Health Outcomes Monitoring System (WHOMS) (466)	Milan, Italy	Cancer patients	Web-based or mobile phone reporting of cancer pain; information to clinician	Clinician only
University of Washington Cancer Website Research Project (467-469)	University of Washington	Cancer patients treated with radiation therapy	Internet-based application administered via touchscreen; information to clinician	Clinician only

Despite guidelines (399,401), the routine use of PROs has been slow to implement in clinical practice, in oncology as well as palliative care (400,472,473). Their optimal application is yet to be achieved (427). No system of routine PRO collection and especially longitudinal tracking of HRQOL is currently in place for multiple myeloma. Due to the relatively long median survival time, many patients classify as cancer survivors (474-477) and might benefit from self-monitoring, especially during stable phases in which they do not receive treatments. This could help patient empowerment (38). This PhD study aims to describe the longitudinal trajectory of symptoms and HRQOL in these patients. The longitudinal information on HRQOL will also be

used to test which items perform best for the purpose of routine self-monitoring, thus indicating which variables might be validly and reliably monitored in multiple myeloma.

2.2.4 Measurement of quality of life in multiple myeloma

The previous section demonstrated some of the challenges of using PROs in clinical practice. The subjective nature, often leading to considerations of PROs as 'soft' endpoints, methodological limitations regarding the interpretation of scores of individuals, real-time data collection and missing data can pose barriers to the routine use of PROs. Particularly in the context of supportive and palliative care, clinical relevance and feasibility is of importance, meaning short and simple measures that are easy to score and interpret and that are able to assess change in individual patients over months and years (316). The clinical utility of a measure is determined by its measurement or psychometric characteristics (478). During the validation, particular emphasis needs to be placed upon making sure that the questionnaire works in the population in which it is intended to be used.

In multiple myeloma, clinical applications of PROs can be manifold, aiding prognostication, monitoring response to treatment and prioritising problems or facilitating communication (38,316,479). Due to the often substantially reduced QOL in myeloma patients, some authors have called for making HRQOL assessment a normal part of clinical haematological care (32,34,35). Despite these demands, a systematic review identified 13 HRQOL instruments, none of which had been specifically validated for its clinical applicability (359). Most importantly, when contrasting available tools with results from qualitative studies identifying issues important to myeloma patients' QOL (310,361,385,480-482), no instrument was comprehensive to all issues important to patients. This challenges the content validity and face validity of some of these tools. The EORTC QLQ-C30 (22,29-32,36,242,364,368,375,382,483-491) and QLQ-MY24/20 (221,310) were the questionnaires which had undergone the most comprehensive psychometric evaluation. The other HRQOL questionnaires validated in myeloma were: the EORTC-QLQ-High-dose chemotherapy module (HDC-19) (29,221,492), the FACT-G and anaemia (FACT-An) and bone marrow transplantation (BMT) modules (35,185,493,494), the Short Form-36 and SF-12 (34,495-497), the SEIQoL (30,490), the EuroQOL-5D and 15-D (36,382), the Life Ingredient Profile (originally for leukemia patients) (498) and Ferrell's Quality of Life Index (486). Most studies validated tools in clinical trial populations and not in clinically representative groups (359). There was considerable variation in the domains within the multi-dimensional HRQOL framework included in the tools and a wide spread of health status and health evaluation scales (295).

For defining clinical utility, areas of item development and item validation need to be taken into account. A clinically useful measure should have good content and face validity (316) and capture the core domains that patients find most important to their HRQOL. In multiple myeloma, a set of core symptoms comprising the most common symptoms that are either disease- or treatment-related are essential for monitoring the disease status (e.g. asymptomatic patients versus patients with active disease) (26,61,71). These core symptoms should include pain, bone pain, and fatigue, but also gastrointestinal symptoms, symptoms of the neurologic and musculoskeletal systems and signs of bone marrow involvement, to cover the most common side effects of treatment (9,58,87,89,92,499-507). The HRQOL tool should cover symptom burden as the subjective evidence of disease observed by the patient (508,509). There is value in focusing on specific myeloma symptoms in some contexts, but there is also value in building a tool using common symptoms to enable cross-study comparisons with other conditions (510). A core set of 12 common symptoms that affect most cancer patients has been defined in oncology (511). These two poles – the instrument covering only common symptoms or covering disease-specific symptoms – can be partly harmonised by using a core list of symptoms and adding disease-specific symptoms at the end. Another option is to use free-text fields to add other symptoms and problems not contained in the fixed list (512). Since symptom management has been identified as one of the areas of need in multiple myeloma (369), accurate and psychometrically sound assessment of symptoms can form the first step in addressing this gap.

Furthermore, a clinically useful tool should incorporate issues that diminish QOL but are seldom discussed in clinical consultations between patients and clinicians due to their embarrassing nature. These can comprise personal aspects of the illness experience such as anxiety, uncertainty and sexual function, but also cognitive problems (90,507,513). Underreporting and under-detection of symptoms in clinical contexts that do not use patient self-report have been described in many studies (412-414). This does not only concern symptoms but also QOL problems (514-516).

Limited clinical utility of QOL instruments in multiple myeloma also stems from the fact that most of these tools are validated only in the early stages of disease but not in the advanced or palliative setting. The domains of QOL that are important to patients during later stages of disease most likely differ significantly from those at diagnosis or in stable disease (383). The exclusion of patients with relapsed disease or validating a HRQOL in clinical trial groups poses the additional problem of leading to a biased sample that is not clinically representative of the wider patient group (517). Combined with this aspect is the problem of QOL questionnaires in multiple myeloma mainly assessing health status (359). However, the presence or severity of a problem does not indicate how much that problem impacts on the patient's QOL, as was detailed in the qualitative study of myeloma patients (357). A severe symptom or problem might not have a large

impact on QOL, even if biological and clinical parameters indicate that it should (518,519). The distinction, along with the theoretical model of QOL, ultimately becomes important when trying to identify targets for supportive care interventions in multiple myeloma. For example, going back to Fayers and coauthors' distinction between indicator and causal variables (339,340,356), if symptoms are defined as causal variables, directly causing poor QOL, treatment would be directly targeted at the symptom. If, however, symptoms are indicator variables, treatment would need to be directed at other aspects of HRQOL, such as emotional well-being (520). These distinctions play a role in myeloma as some of the symptoms, in particular fatigue and depression, are reflective of QOL (indicator variables) while other symptoms may be causal variables (e.g. poor mobility) (357). This can be communicated via the scale that is used to assess these components (518,519).

A related issue is the distinction between needs, satisfaction and HQOL. HRQOL surveys capture how well the patient is doing in several domains. Satisfaction measures focus on how well a particular clinician or organisation delivered healthcare (521). Another group of measures concerns supportive care needs (476,522-531). Needs are usually indicators of deficit and have been defined narrowly as the capacity to benefit from healthcare (532). This introduces the problem that wider aspects of HRQOL may not be seen as needs of the individual in case of healthcare not being able to address these areas of the patient's experience (such as personal and environmental characteristics but also fatigue or difficult-to-treat symptoms) (533). A myeloma questionnaire asking about supportive care needs may thus not have clinical utility if these important areas are missed, leading to diminished content validity. Rather, it is for instrument developers to also provide guidelines for clinical management of these QOL-related symptoms and problems (531,534). Needs assessments have recently been used in myeloma care (535), but are usually conducted at one point in time. Since clinical utility entails using the HRQOL tool as an outcome measure and outcome measurement per definition requires longitudinal measurement (448), cross-sectional needs assessment forgoes aspects of change. It is longitudinal validity that helps the applicability of the measure in routine clinical practice. Only if changes can be validly and reliably tracked over time, HRQOL can function as an outcome measure.

Based on the findings from the systematic review and qualitative study, the research group at the Cicely Saunders Institute developed the Myeloma Patient Outcome Scale (MyPOS), a HRQOL measurement tool particularly geared towards its use in routine clinical practice (see section 4.3) (384). The questionnaire was designed to address some of the shortcomings identified in the systematic review. For clinical applicability in particular, the MyPOS was designed to have good content and construct validity (357). This PhD study aims to validate this measure for longitudinal monitoring of HRQOL and symptoms in multiple myeloma.

2.3 Conclusions from the literature

What is known about quality of life in multiple myeloma?

- Myeloma as an incurable disease places a high burden on patients. There is evidence that myeloma patients suffer from more problems and symptoms than patients with other haematological cancers.
- There is a dearth of longitudinal evidence. Only four observational studies so far have measured changes in symptoms and HRQOL in patients receiving chemotherapy or stem cell transplants. There is no longitudinal information for patients receiving maintenance treatment or no treatment and no information on the impact on quality of life in the advanced, progressive stages of the disease.
- Multiple myeloma is underserved by palliative care due to several barriers: the sudden death of patients and scarcity of prognostic indicators, attitudinal barriers in haemato-oncologists that lead to late referrals and the lack of discussion regarding goals of care. Early integration of palliative care in multiple myeloma could be feasible if appropriate screening and monitoring of palliative care needs is introduced.

What is new about this project?

- This study follows a natural sample of patients at various stages of the disease and receiving different treatments over time. It will allow a description of the course of symptoms, HRQOL and psychological distress over time and in the advanced stages of myeloma.
- The study aims to identify predictors for poor QOL and high palliative care concerns, which will allow the development of a model of prognostic indicators for palliative care involvement.
- Recent attempts to incorporate PROs such as QOL into routine clinical practice have yielded mixed results. One avenue that has not been explored is monitoring QOL in multiple myeloma. For this, psychometrically robust items need to be selected which should satisfy more stringent criteria in order to measure individual changes validly and reliably.

What is the clinical applicability of the results?

- One barrier to the integration of supportive and palliative care services in multiple myeloma is the unpredictability of the illness trajectory which renders prognostication difficult. Describing symptom patterns, distress and QOL over time will help

identification of trajectories and help determine whether these outcomes can be used to diagnose deterioration. Demographic, clinical and treatment-related predictors for poor QOL can help define the clinical profile of those in need of supportive or palliative care services and can help target therapies specifically to this group.

- Knowledge of predictors for QOL will help identify those items or subscales that have high predictive validity in this patient group. Further item testing of the MyPOS can yield a small set of questions that could be used by patients themselves to monitor changes and could help direct them to support and services in a more timely manner.

3 Aims and objectives

3.1 Aim

The aim of this study is to describe, understand and compare the individual QOL and symptom trajectories of people with multiple myeloma over time and to evaluate the validity of the Myeloma Patient Outcome Scale (MyPOS), a myeloma-specific questionnaire to measure QOL and palliative care concerns, for longitudinal patient-monitoring.

3.2 Objectives

1. To determine the prevalence and severity of common symptoms and problems in patients with multiple myeloma at various stages of their disease, specifically for those with relapsed or progressive disease, and to determine whether patients in the advanced stages of myeloma experience a different symptom and problem profile than patients in earlier stages.

2. To determine demographic and disease characteristics that are associated with poor quality of life and high palliative care needs and evaluating whether general symptom burden has a stronger influence on poor QOL and/or high palliative care concerns than demographic and disease characteristics in a cross-sectional sample of myeloma patients.

3. To identify the intra-individual change trajectories of QOL among multiple myeloma patients at various stages of disease over a period of 8 months. I hypothesise that four or five subgroups of individual QOL trajectories exist, defined by patterns of stability, improvement or deterioration and with a different initial level of QOL (good versus poor).

4. To evaluate whether general symptom level and demographic as well as clinical characteristics help predict who experiences a deteriorating QOL or chronically poor QOL trajectory.

5. To evaluate the validity and item quality of the MyPOS and its scale in myeloma patients at different stages in their disease trajectory in order to identify the items or subscales from an item pool that are the most reliable and valid for monitoring intra-individual changes in health-related quality of life in myeloma.

6. To identify the items or subscales that have the best item characteristics, longitudinal reliability, validity (responsiveness to change) and for monitoring health-related quality of life in myeloma.

4 Methods

4.1 Introduction

In this chapter, an overview of the methods used in this PhD study is presented. The detailed methods used for each component are described in their respective publications and chapters (see chapter 5, 6 and 7). The methods are further detailed in the study protocol that was prepared for the ethics application and can be accessed in Appendix B. The focus in this chapter is to give an overview and to describe the conceptual framework that links the three parts of this study.

4.2 Overview of study design and methodological considerations

In Figure 6, an overview of this PhD study is presented that shows how phases of this research interlink and how data from previous phases inform subsequent phases and are integrated to answer the objectives of this study. Figure 7 shows how datasets interlink. The heart of this PhD project is a longitudinal survey of symptoms and HRQOL in patients with multiple myeloma. The longitudinal study provides data both for modelling trajectories of HRQOL and for identifying predictors for poor QOL, thus answering the question of who is at risk of experiencing a deterioration in their health status. It also provides the main dataset for identifying those items from the MyPOS that are suitable for individual patient-monitoring. The model of predictors is built in several steps. Preliminary phases include systematic review and meta-analytical work to identify and understand the respective strength of variables influencing QOL in this condition. This initial model of predictors is supplemented by a review of the symptom burden and prevalence of HRQOL problems (presented in chapters 2.2.2.1 and 2.2.2.3, respectively). These models inform subsequent selection of variables in the regression analyses. A first model is built on the basis of a secondary dataset, involving a large naturalistic sample of multiple myeloma patients from multiple centres. For the secondary analysis, the dataset from the initial validation of the MyPOS is combined with the baseline dataset from the longitudinal PhD study. Methods for prioritising and selecting variables into the prediction model are detailed below. This model is then partly validated and extended by taking more variables from the longitudinal study into account. Also, the longitudinal trajectory of the outcome variable is modelled. Information from the regression analyses is finally integrated with the information on the suitability of items for longitudinal monitoring to develop a system of outcome variables to monitor in multiple myeloma. In this last step, a set of common, easy-to-measure variables is identified that could potentially be used as indicators for early palliative care involvement in multiple myeloma.

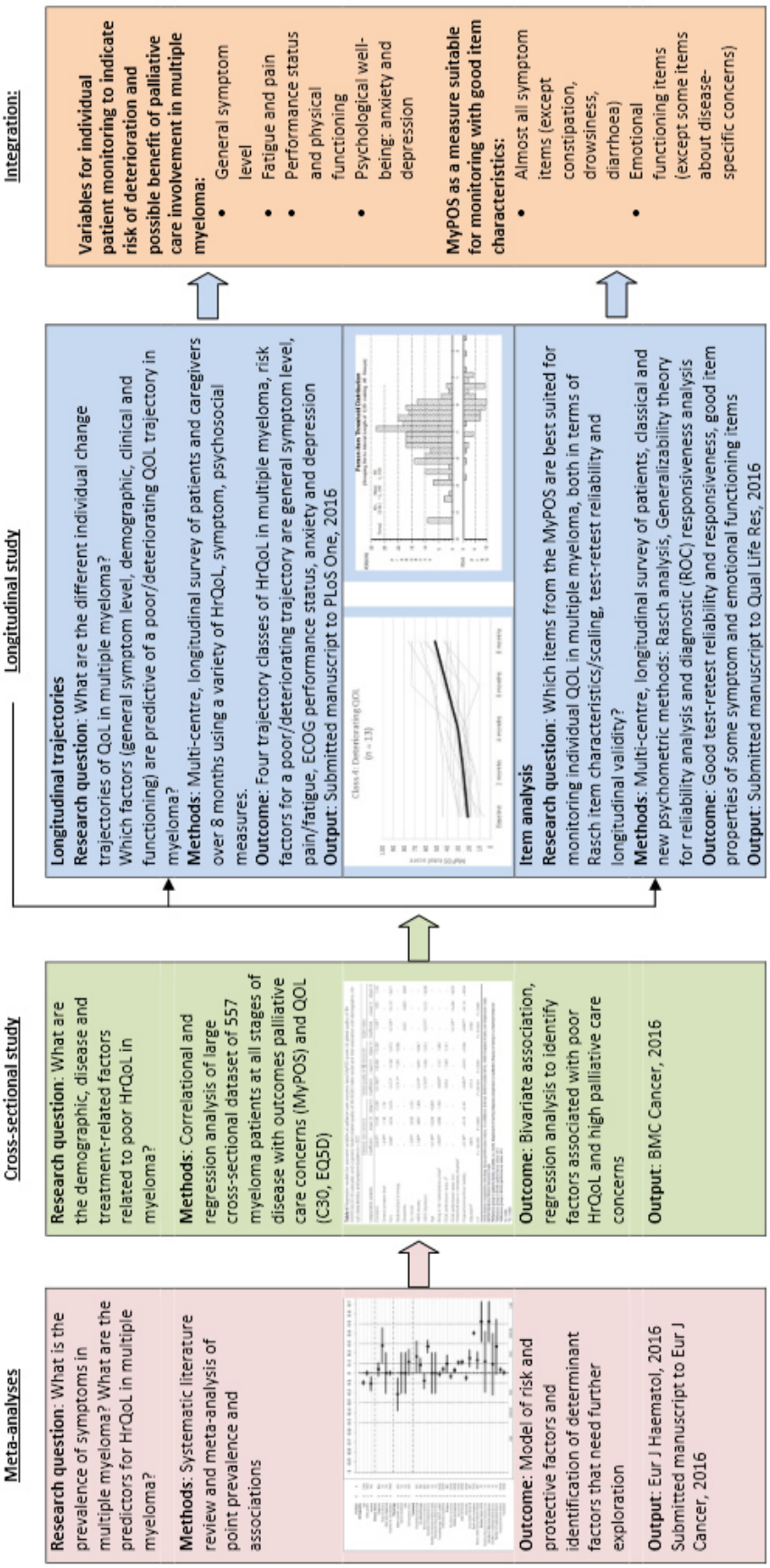
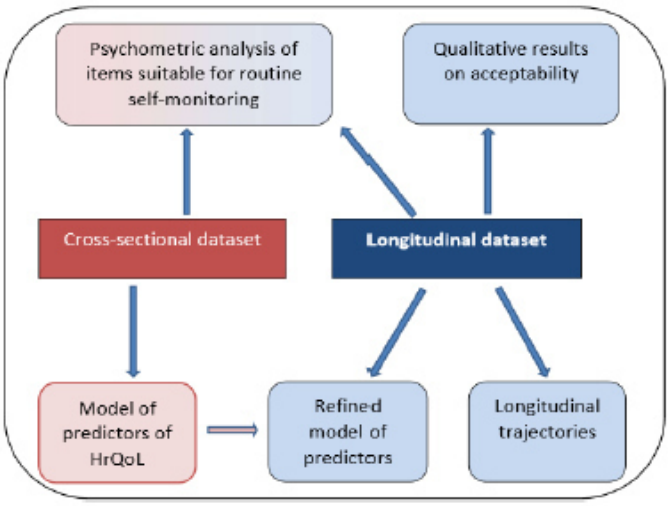


Figure 6: Overview of the PhD study and integration of findings from different substudies

Figure 7: Overview of datasets used in the PhD project and outputs



4.3 Research questions and rationale for study phases

In the following sections, I present the rationale for the study phases and methods used. Detailed information with an overview of the methods of data collection and analytical approaches that were used in the study phases is given in the results chapters and the study protocol, Appendix B. Appendix D and Appendix F contain the study information leaflets, consent form templates and questionnaire booklets that were used in recruitment and data collection.

4.3.1. Phase 1: Cross-sectional, secondary analysis

The research questions for the first phase of this research study are:

1. What is the prevalence and severity of symptoms and palliative care-related concerns in patients with multiple myeloma at various stages of their disease?

2. Do patients in the advanced/progressive or refractory disease stage experience a different symptom and problem profile than patients in earlier stages?

3. Which demographic, clinical and treatment-related factors are associated with a lower quality of life and more symptoms and problems?

4. Do the general symptom level and specific symptoms have a stronger influence on health-related quality of life than demographic and disease (biomedical and treatment) factors?

Since 5-year survival has increased from 24-32 months to 68 months in multiple myeloma, patients are now living longer with the complications of their illness, treatment-related short- and long-term toxicities and possible comorbid conditions (58). Clinical decision making should increasingly be driven by QOL-related concerns and it has been recommended that QOL assessment becomes part of routine care in this incurable condition (32,34,35). The systematic literature review of symptom burden in multiple myeloma (see section 2.2.2.1) yielded high prevalence rates for different symptoms, thus showing that patients face profound symptoms and emotional, social, and financial consequences associated with the cancer (536). However, it also became apparent that robust information on symptom prevalence is rare in myeloma, with mainly clinical trials or studies in mixed haematological SCT samples contributing data. There is also a paucity of studies focusing on the advanced stage. The burden of symptoms close to the end of life is therefore unknown. This study phase addresses this gap by determining symptom prevalence in patients at various stages of their disease.

The research questions address objectives 1 and 2 (see chaper 3, Aims and objectives). This study phase focuses on the analysis of a combined dataset of two studies to give a cross-section of the prevalence of common symptoms and problems. Combining the dataset from the validation study of the MyPOS with the baseline of the longitudinal survey data from this PhD study resulted in a large dataset with enough power to answer the research question and to yield robust results for exploratory modelling of predictors (see 4.3.3, Phase 3 – Regression analysis/prognostic model). As the aims of the current analysis differ from the original aims of the MyPOS validation study, new questions will be asked of the data, and a secondary analysis will be performed (537-539). The use of secondary analysis has methodological, analytical and ethical implications.

Simply put, secondary analysis is a set of research endeavours that uses existing data to answer research questions that may not have been proposed when the data was originally collected (540). Because many studies contain more data than is analysed in the primary study, and secondary analysis has the potential of yielding much higher sample sizes that are large enough to enable the investigator to draw meaningful conclusions, its use has been advocated for both quantitative and qualitative descriptive studies in palliative care (541,542). This approach is different from meta-analytical studies in which effect sizes are estimated from means or count data in original studies, but a synthesis of estimates from original data is usually prepared under the same original aim. Descriptive studies, in which the portrayal of the characteristics of a group of patients, determining the frequency of events or the correlational, systematic investigation of relationships between variables are the key focus, lend themselves to secondary analysis. Secondary analysis can uncover aspects of a research problem that can lead to hypothesis revision or revision of existing measures (543,544) and the analysis of existing data can serve as a pilot study leading to the generation of new hypotheses (544,545). Both of these aims are addressed by combining

baseline data from this longitudinal study with data already collected. This study phase provides data for the initial development and exploratory analysis of symptom prevalence and the correlational model of variables associated with poor QOL in myeloma. Both of these aspects inform the descriptive component of understanding trajectories of symptom burden and QOL in the longitudinal study, and forming the first phase in building a prognostic model of QOL predictors in the survey. This initial phase should not be considered a pilot study per se, as its aim is not simply testing study procedures, validity of tools, estimating the recruitment rate or estimating parameters needed for sample size calculation (546). Although it partly aims at providing the mean and variance estimates for sample size calculation in the longitudinal survey, it rather forms the initial step in a hierarchy of study phases to help model the factors associated with poor QOL that could potentially reveal targets for early palliative care intervention. This phase also serves the generation of hypotheses, particularly regarding the role of the general symptom level as an independent factor to explain poor or deteriorating QOL in multiple myeloma.

Many approaches to secondary data analysis have been described (547). Among the most common are: taking a unit of analysis different than in the original study, studying a subsample, studying a different relationship between variables in the study (designating a new dependent variable), changing the method of analysis and analysing data that was collected but not analysed in the original study (547). This secondary analysis follows the latter three approaches with using the demographic, clinical and outcome data collected in the MyPOS validation study with three new dependent variables, the MyPOS total score, the EORTC QLQ-C30 global quality of life subscale and the EuroQOL EQ-5D Index score. The method of analysis was changed from establishing reliability and validity of the MyPOS to analysing prevalence and correlational/regression analysis. Thus, data that was collected but not analysed in the MyPOS validation study (e.g. the EQ-5D Index score, clinical information on staging of the disease and treatment details) is taken into account in this secondary analysis.

Secondary analysis is a systematic method with procedural and evaluative steps. Like any research, the research question determines the research and analysis method (548). Hence, the first step in the process is developing the research questions. After identifying a suitable dataset, the next step is the evaluation of the dataset to ensure its appropriateness for the research topic (539,549-551). To make sure that the dataset addresses initial requirements, it is recommended to outline the original study, the process of data collection and the analytical processes applied to the data plus making processes regarding missing data transparent (552). The fit between the primary dataset and the research question is essential (552,553). To ensure congruency and quality of the resulting analysis, the following questions should be asked: (a) what was the purpose of the study, (b) who was responsible for collecting the data, (c) what and when and how the information was

obtained (551). This framework can be extended by examining data collection techniques in the original study more closely to judge the internal validity (sample and measurement bias) and external validity (generalisability, representativeness). By evaluating (1) the definition of the target population and representativeness of the sample (i.e. sampling method), (2) the eligibility criteria, (3) strategies used to minimise selection bias, (4) methods to prevent study attrition, (5) characteristics of non-responders and drop-outs, (6) validity and reliability of the data collection instruments, (7) controls used to minimise threats to measurement bias, and (8) procedures for handling missing data in the original research study, the scientific quality of the analysis can be described.

Only one of the two primary datasets accessed for this secondary analysis was collected before the start of the longitudinal PhD study. The second dataset with which it is combined represents primary, original research. Dataset one was collected in the same population as dataset two, the baseline (cross-sectional) data from the longitudinal MyPOS study. In fact, data collection for the longitudinal study almost directly followed data collection for the MyPOS validation study in the participating centres. Data for both studies was partly collected in the same NHS trusts which resulted in study participants taking part in both studies. In case of duplicate ID numbers, newer data was kept in the analysis. Hence, the definition of the target population was the same in both studies, with the same sampling method (consecutive sampling) followed and thus with the same issues around representativeness. Consecutive sampling on the one hand aids representativeness by avoiding narrow eligibility criteria (as are necessary in clinical trials (554)), but also diminishes external validity by oversampling fitter patients that are more satisfied with the quality of services (147,555,556). Gate-keeping will also have affected data collection in both studies in the same way as there is an overlap in study personnel recruiting and collecting data in both studies. The MyPOS validation study was a three-year study, funded mainly by Myeloma UK, which aimed to develop and psychometrically validate a new, myeloma-specific quality of life measure. 380 patients with a confirmed diagnosis of multiple myeloma and not too ill, symptomatic or neutropenic to take part were recruited from 11 secondary and tertiary care centres in the United Kingdom. The study recruited consecutive patients whereby all available myeloma patients were screened for eligibility at every outpatient clinic or ward where recruitment was active. Data collection took place between May and August 2013. Participants who declined participation were asked for consent to record limited demographic details to judge the extent of sampling bias. Participants received a questionnaire that consisted of the following measures: Myeloma Patient Outcome Scale (MyPOS), EORTC QLQ-C30 and MY20 and the EQ-5D-3L. Participants were given the option to complete the data collection instruments in the clinic or at home, returning them by post. Clinical data were collected by the research site staff, consisting of demographic characteristics, disease stage and phase, treatment history, and ECOG

performance status. Data was analysed using exploratory and confirmatory factor analysis and examining construct validity in form of subgroup comparisons and correlational comparisons to other measures (384).

The definition of the target population, criteria for inclusion and exclusion and strategies to minimise selection bias were the same in the two datasets (quality criteria 1-3 above). Methods to prevent study attrition were also comparable between the two datasets. In the MyPOS validation study, participants failing to return their questionnaires from home received a reminder phone call after one week. Since participants were given a pre-stamped envelope for returning questionnaires to the study centre, attrition was low in the MyPOS study. Only 21 of 401 recruited participants failed to return the questionnaire (see chapter 5). An even smaller proportion of withdrawals was observed in the baseline of the longitudinal survey. Furthermore, selection bias is low in both samples since a comparison of non-responders and withdrawals to the study population revealed no differences in demographic and clinical characteristics (384). Data collection instruments were selected on the basis of their status of having been validated with appropriate psychometric properties in the myeloma population. Regarding the outcome measures, QOL tools completely overlapped between the two studies, as did most other demographic and clinical characteristics. However, since the purpose of the MyPOS validation study was different from that of the secondary analysis, particularly regarding evaluating disease and treatment characteristics in their independent association to poor QOL, the analysis is biased towards patient-reported outcomes as many potential predictors such as haemoglobin level (483,557), albumin and creatinine levels (183), cytokines (186-188) or treatment response status (26,558), were not collected. Minimising measurement bias was achieved by training study site-personnel in study procedures. Some measurement biases, due to participants self-completing questionnaires without assistance, will not have been able to prevent. Procedures for handling missing data were detailed in the original analysis and consisted of returned questionnaires being checked by the investigator for missing items with subsequent phone calls to the participant to elicit an answer to the item. This strategy, although introducing a recall bias, resulted in a very low amount of missing data in outcome variables and symptom items. Demographic and clinical information were extracted from electronic patient records and carry a larger proportion of missingness, as high as 30% in the case of International Staging System (384).

There are ethical considerations when carrying out any research which are relevant to a secondary analysis as well. These issues centre on confidentiality, non-maleficence and fidelity (553). One issue in particular, that of informed consent, needs specific consideration in this context. Secondary analyses of an existing dataset carry the risk of participants not having consented into this use of their data. In the MyPOS validation study, participants consented for their details to be kept on an anonymised database and that the data collected could be used further in an

anonymised form. The secondary research questions presented here were partly generated during the analysis of the MyPOS validation study and were related to the intention of the primary research, namely the description of the burden associated with QOL-related problems and concerns in this sample. Therefore, the judgment was made that the consent gained in the MyPOS validation study covered the goals of this secondary analysis.

Overall, the MyPOS validation dataset represents a valid dataset for combination with the baseline data from the longitudinal survey and shows an appropriate fit for the purpose of the secondary analysis. The research participants and the population to whom the new set of research questions apply are congruent and this congruence extends toward the variables that were measured. The context in which the original data were obtained as well as the target population are also comparable. There are two main benefits of secondary data analysis, scientific advantages and functional advantages (547). Scientific advantages include the inclusion of more variables, the ability to survey a more diverse sample and possibility of more advanced statistical techniques (559,560). This secondary analysis allowed the exploration of symptom burden and QOL in different disease phases and how demographic and clinical variables are related to the outcome, thereby generating and testing hypotheses for the analysis of longitudinal trajectories. Functional advantages include cost-effectiveness, through combining existing datasets and yielding a large sample size sufficient for robust analyses which might otherwise not be feasible (539,549,550,559,561). The main limitation of secondary analysis, collection of original data usually serving a different purpose and the investigator having no control over the data collection process, is mitigated by the investigator being involved in the study design and data collection in both studies. The dataset was easily accessible and the investigator knew the types of variables and type of sample as well as other design issues which increased the fit between the new research questions and the original data.

4.3.2 Phase 2: Longitudinal analysis of the trajectory of quality of life in multiple myeloma

One of the main aims of this study is to examine the quality-of-life experience of individuals living with multiple myeloma over time, considering the core components of symptoms, wider palliative care-related problems and concerns, and coping/adaptation processes. It is also studied how these components interlink with patient characteristics. The first objective is to describe trajectories of the illness experience in this patient group. Second, the co-variation of the components of QOL, particularly aspects of symptoms and functioning, is described, with an assessment how initial patient and disease/treatment characteristics are related to outcomes over time.

The research questions are:

1. What is the prevalence and severity of symptoms and palliative care-related concerns in patients with multiple myeloma over time and when during the observation period is symptom burden and burden from palliative care-related problems highest?

2. Does the patient-reported quality of life experience of this cancer change over time?

3. Are there distinct groups of individual change trajectories within the overall QOL trajectory, so that individuals can be characterized by a change trajectory showing the typical course of QOL for a small, homogeneous group? It was hypothesised to find classes of stable/chronic QOL that would vary by the level of QOL (intercept), either being low, moderate or high. It was also assumed to find classes of QOL experience characterized by an improving or deteriorating trajectory (slope). Further, the existence of a class of potentially fluctuating course of QOL was hypothesised.

In addition, this study also develops a large and comprehensive dataset on burden of care and associated costs, as well as information from informal caregivers on their health, the patient's health and well-being and their perceived caregiver burden. However, these variables are not analysed in the present PhD study and will be the subject of future publications from this project.

Symptoms, HRQOL and other variables are assessed longitudinally using an analytic postal survey method with follow-up data collection every two months for patients with multiple myeloma. This study uses a panel sample (follow-up of the same population) and recruits participants from 12 secondary and tertiary hospitals in England. The advantages of longitudinal designs lie in their ability to capture change and to examine these changes in relation to patient characteristics. It is the only design that allows the establishment of temporal relationships between independent factors and outcomes (562). Due to the observational nature of this study, results are more representative of the underlying population than evidence from experimental studies with more strictly defined eligibility criteria (554).

Understanding symptoms and other aspects of the illness experience over time has shown to be one of the main study designs to address those gaps in the palliative care evidence that are needed to inform how health and social services can best provide care to individuals with a life-limiting diagnosis. Improvements in the management of multiple myeloma mean that patient live with their disease for longer, thus experiencing accumulated symptoms and problems from myeloma itself and its treatment. Knowing about the progression of these QOL-related symptoms and problems over time allows better targeting of assessments, review times and referrals to supportive care services at times of high patient or family need. Thus, longitudinal information

can inform follow-up. If a large enough sample is recruited, subgroup analyses can help determine distinct trajectories of QOL experience in multiple myeloma and thus identify who is at risk of experiencing poor subsequent outcomes. Consideration of trajectories of symptoms and QOL problems can help with advance care planning, by helping to anticipate likely physical and psychological needs (563). The need for advance care planning is particularly high in the group of myeloma patients, due to this disease being life-limiting from the start of treatment, yet being subject to the pervasive culture of cure that precludes palliative care involvement (105). Knowing about the progression of the disease and about indicators of times of high need could help clinicians initiate discussions about end-of-life issues and patient preferences earlier. Ultimately, it could prevent unnecessary aggressive treatment at the end of life (564). Knowing about the likely trajectory of symptoms and problems also helps patients and their clinicians to make informed decisions about treatment and may be empowering to patients and their families (565). Understanding symptom trajectories is also the prerequisite for developing interventions and evaluating their effectiveness (566-568). The longitudinal measurement of HRQOL in multiple myeloma in particular can shed light on early intervention targets that could help improve long-term HRQOL impairment, as well as the potential of PROs to act as predictors for long-term mortality (569). From these predictive models, further interventions specifically targeting patients at risk of deterioration and possibly the early integration of palliative care into haematological care could be developed (189).

In palliative care, most of the information on patients' and carers' experiences and needs at the end of life is derived from cross-sectional studies rarely using PROs (259,570,571). The longitudinal studies available in palliative care research usually examine the period immediately before death (259,572-577), but there have also been publications of trajectories at early stage disease (578) and at treatment transition points (572). However, this information can only partly be transferred to multiple myeloma. In palliative care, much attention has been given to the functional decline that accompanies cancer. Three types of common trajectories have been described for three disease groups: a trajectory with steady levels of functioning up until a clear terminal phase for cancer, a trajectory with gradual decline, punctuated by acute exacerbation with subsequent recovery to a level below prior functional ability for organ failure; and a trajectory with prolonged and gradual decline which is typical for frailty and dementia (157). However, functional status can only be regarded a proxy for QOL. Its popularity partly stems from the fact that chemotherapy trials use functional status. Lynn and Lunney's model was developed using cross-sectional data taken at different time points (157). Therefore one cannot be sure that these trajectories reflect the experiences of individual patients over time. Moreover, since the myeloma population has aged and treatments have evolved, concomitant comorbid disease and treatment toxicities accumulate. This most likely results in the trajectory not

following the typical course of cancer. The model also assumes homogeneity of trajectories for different aspects of QOL. Murray and co-authors have shown that different trajectories for subdomains of QOL may well exist that are not related to physical wellbeing. They described a trajectory of spiritual distress that followed a course of several peaks at diagnosis, at recurrence and in the terminal stage (579). They also mapped psychological and social trajectories. Thus, mapping not only the overall mean trajectory of QOL but obtaining a more fine-grained picture can help identify those patients within the myeloma population that would benefit from palliative care involvement. Such data could help with the early integration of palliative care alongside curative treatments and replace the idea that palliative care is confined to the last few weeks of life (equating with end–of-life care) (565). The palliative care approach could support people with chronic progressive illnesses much earlier and over many years.

In this PhD study, multidimensional trajectories will be plotted. Therefore, this study aims to recruit a diverse sample including a spectrum of disease trajectories (shorter/longer, stable, fluctuating and deteriorating), with changes in QOL due to cancer, treatment, comorbid health problems, with periods of relapse and refractory disease. This will provide a broad dataset with data applicable to the wider population affected by multiple myeloma and possibly similar chronic, incurable haematological cancers (like myelodysplastic syndrome (MDS), chronic myeloid leukemia (CML) or follicular lymphoma). Longitudinal studies require a careful definition of the groups for study and a careful selection of variables for measurement (580,581). This study recruits a consecutive sample from out- and inpatient clinics. By recruiting patients that are in secondary and tertiary care, a more representative sample can be gained than studying treatment populations only (83,147). The timing of the repeated survey points should occur when changes are expected. This is difficult to realize as the population of myeloma patients is diverse (see Background Chapter 2.1). No concrete guidelines exist for the timing of HRQOL measurements. A study in non-small lung cancer patients advised a three-week interval for QOL assessment (582). Other guidelines (583,584) for timing of measurement in oncology mainly focused on advanced, palliative samples and therefore advise up to weekly data collection to counteract the high attrition that can be expected in that population. However, patients with multiple myeloma have a median survival of several years. To strike a balance between capturing changes and keeping participants engaged with the study, bi-monthly data collection is proposed as appropriate.

Selection of variables for measurement is based on a prior cross-sectional survey of the same population and those measures that have been validated in multiple myeloma have been chosen for this study (359). Postal surveys require least effort for the participants and are among the cheaper alternatives for costly longitudinal studies (581). However, response rates need to be high and attrition needs to be factored into the sample size calculation. Longitudinal research can suffer

from poor recruitment and retention (585). In designing methods of approaching potential participants and study procedures like telephone support and postal surveys in this study, results from qualitative studies that used semi-structured interviews to identify the views on taking part in longitudinal research and the preferred methods of approaching and contacting study participants (585,586) have been taken into account. Furthermore, in its pilot phase this study used qualitative interview methodology to explore the best methods of recruitment and longitudinal follow-up. The topic guide for these interviews is shown in Appendix E. After conducting and analysing five interviews from purposefully sampled patients, no changes to the proposed methods for the longitudinal component of this PhD study were needed. Therefore, no further interviews were conducted and we proceeded to the next phase of research.

The longitudinal modelling framework consists of two components: within-person change and inter-individual or between-person change. The former answers the question how symptoms and QOL dimensions of each study participant change over time. The latter answers the question of what predicts differences in the symptom and QOL trajectories among individual participants (587). Thus, the analysis separates the descriptive mapping of trajectories from the relational and analytical part, the examination of associations among explanatory variables and trajectories (587). The two main benefits of longitudinal analysis are its capacity to understand individual within-person relationships while at the same time providing the opportunity to test hypotheses at multiple levels of analysis (588). The fundamental tenet of longitudinal analysis is that these two elements need to be separated in the analysis. Relationships that are observed at the within-person level need not mirror those observed at the between-person level of analysis. Hypotheses for both levels should be formulated separately (589).

Collins (2006) (590) and Collins & Graham (2002) (591) define three elements of any longitudinal modelling framework: the theoretical model of change and the temporal design used to observe the change phenomenon, both of which need to be reflected in the statistical model of change. The first element, the theoretical model of change consists of a clear statement about the nature of the change phenomenon that is observed. This concerns a description of the shape of change (stable, rising, curvilinear or fluctuating), a possible cyclical nature of change, and which time-invariant and time-varying covariates may predict change. The temporal design involves decisions about the timing, frequency and spacing of observations in the longitudinal study (591). These decisions presuppose the statistical model that is chosen for analysing longitudinal change in individuals (590). Since multiple myeloma is a heterogeneous disease as to the clinical manifestations of disease-related problems and as to the treatment pathways that patients experience, in this PhD study both the observation of within-person stability and within-person fluctuation is expected. The temporal design chosen is a compromise between not placing too

heavy a burden on study participants, yet trying to capture outcomes often enough to detect significant stages of change in a sequential process of change (591).

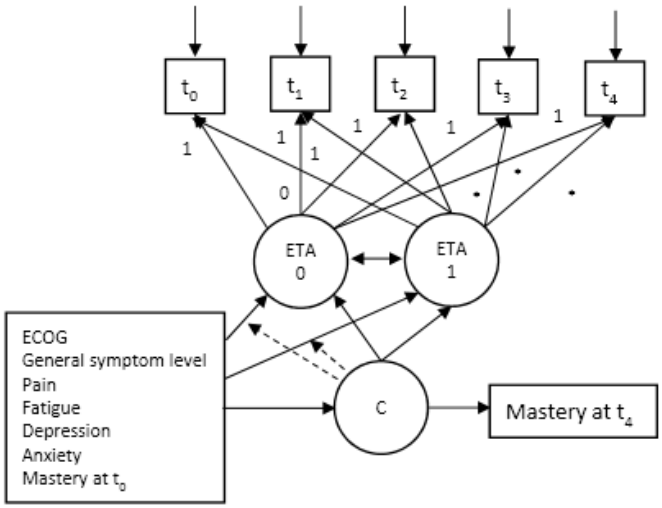
In terms of the statistical model of change, one goal of this research study is to adequately capture the variation within and between individuals. Instead of establishing a general developmental trajectory for all participants in the study, understanding change within the individual and establishing intra-individual variability is the primary interest (592). Most often, trajectory studies focus on establishing an average change trajectory for the entire group by first plotting individual trajectories of all participants, then estimating an average/mean trajectory from the mean symptom or QOL scores at each time point. However, given the conflicting results of those few studies having examined changes in QOL in multiple myeloma (see section 2.2.2.2), one can presuppose considerable heterogeneity within the QOL trajectories of multiple myeloma patients. Inconsistencies in the conclusions of these longitudinal studies, ranging from reporting decreases in psychological symptoms and QOL-related problems (31,35) to studies concluding substantial worsening or deterioration (381,593), may stem from the fact that analysis of change made use of mean symptom or QOL scores for the entire sample. Conventional approaches to modelling the longitudinal course assume that individuals are sampled from the same underlying population and that a single growth trajectory can describe the entire sample. These approaches are usually known as random-coefficient or mixed linear regression models (594-596), sometimes also described as multi-level or hierarchical models (597). In these models, although each participant is assumed to have his or her own unique trajectory, a single group, fixed coefficient is computed to index the average rate of change for the entire sample (386). Between-subject covariates are then introduced into the model, either as fixed covariates (e.g. demographic variables, baseline variables) or time-varying random covariates (e.g. time-varying physiological variables or psychological/coping variables). Although this is a very flexible and robust method for analysing change that allows imbalanced data (measures not collected at the exact same time point for each participant) with missing values (594-596), it disregards the existence of potential subgroups whose trajectory may be significantly different from the overall estimate. Moreover, covariates are further assumed to affect the trajectories of all individuals in the same way, an assumption that might not hold true in myeloma, a disease in which certain predictors may only be relevant for certain patients at different stages in their disease (598).

These problems in statistical longitudinal modelling have been captured in the distinction between person-centered and variable-centered analytical methods (599). Variable-centered approaches such as random-coefficient models, other models like generalized estimating equations for non-parametric data (600) focus on describing relationships among variables. The aim of such analyses is usually to understand relationships between independent and dependent variables. Person-centered approaches, on the other hand, bring together methods of cluster analysis with

mixed effects models and focus on relationships among individuals, with the goal being the classification of a heterogeneous group into distinct subgroups based on a homogenous individual response pattern (601,602). This results in the analysis separating classes of groups of individuals that are characterised by a common pathway of QOL-related problems. Person-centered approaches are therefore better suited to address individual differences in patterns of change over time (603). These models are known as latent growth curve analysis (LGCA) (601,602), or in the presence of within-class variance on growth parameters (slope and intercept), as growth-mixture modelling (GMM) (601,604). In an LGCA model, two types of hypotheses can be posited. The first set of hypotheses usually concerns the number of latent classes, i.e. distinct subgroups, within the heterogeneous population on the outcome that one is measuring. For the multiple myeloma population, hypotheses can be formed about classes that represent stable QOL, improving or deteriorating QOL and fluctuating QOL trajectories. In addition to assumptions about the slope of the change, hypotheses can also focus on the intercept parameters, i.e. positing high or low values of QOL. The second set of hypotheses then concerns time-invariant or time-variant variables that predict membership in a specific class of QOL change. Variables can be selected that reflect different levels of factors, for example individual factors (such as demographic or clinical characteristics) or system-level factors (such as health service provision or treatment variables) (605,606). It is at this step at which a theoretical model of QOL and its influencing factors can be brought into the analysis, by selecting and hierarchically entering covariates representing the different levels of the QOL model. This approach essentially uses elements of variable-centered approaches like structural equation modeling (607). The results are separate growth models for each latent class, each with a unique set of estimates of influences from independent variables (608).

The latent growth curve model that is tested in the longitudinal component of this PhD study can be depicted in the following way (Figure 8). The growth factor (slope) and intercept parameter (estimated baseline value of the outcome, i.e. high or low levels of QOL) (eta 0 and eta 1 in Figure 8) are modelled to capture changes for the time intervals two, four, six and eight months (t_0 to t_4). The probability of class membership is adjusted for independent variables (ECOG performance status, general symptom level, pain, fatigue, presence of depression or anxiety).

Figure 8: Hypothesised growth model diagram for HRQOL changes over 8 months in patients with multiple myeloma. Square boxes: observed variables; circles: latent variables; directed lines: regression equations.



Several alternative statistical approaches that could be used to model change in this sample were initially explored at the time of planning the longitudinal study, but eventually discarded once the nature of the sample (large enough sample and moderate attrition) became apparent. In the initial stages of this research, the usually small sample sizes common in palliative care research (609) led to proposals of using graphical methods to depict trajectories (587), or using aggregated measures that summarise repeated assessments into a single measure (610). This can either be done by calculating the area under the curve (AUC) (610) or event history analysis (Q-Twist, an approach that calculates the time until deterioration of QOL for each individual in the sample (611)). Summary measures of change can then be subjected to the conventional methods of regression analysis or ANOVA to identify independently associated variables (610,612). However, although summarizing longitudinal change for each subject into a single numeric index can be a powerful method if presented with small sample sizes, longitudinal modelling that takes into account the fact that successive QOL assessments by the same person are auto-correlated are stronger. A technique that can analyse the heterogeneity within individual trajectories of QOL results in higher internal and external validity of findings.

4.3.3 Phase 3: Regression analysis/prognostic model

Research questions:

1. What are the demographic and clinical (disease and treatment-related) predictors of poor outcomes as defined by experiencing a poor or deteriorating quality of life?
2. Do the general symptom level and PROs have a stronger influence on health-related quality of life than demographic and disease (biomedical and treatment) factors?
3. Is the model of predictors robust?

In this study, a system of prognostic predictors is to be developed through a series of regression analyses. First, potential variables for inclusion into the multivariable models are explored in a meta-analysis (see chapter 1.2.2.3). This initial model is then tested on the cross-sectional, secondary dataset and refined and partly validated in the longitudinal dataset.

Within epidemiology and medicine, regression modelling and the investigation whether particular variables are prognostically or diagnostically important and associated with an outcome enables the prediction of patient pathways. Since disease causation is always multifactorial, multivariable models are advised (613-618). Normally, the term prognosis is defined narrowly as the probable course and outcome of a health condition over time (619), as the investigation of causes of disease progression, prediction of mortality risk in individuals or prediction of individual response to treatment (620). In this PhD it is used in a wider sense to include outcomes other than survival and to shed light on deteriorating QOL as an indicator for palliative care involvement. Altman & Royston (614) have used the term more loosely to include other outcomes than survival as well. Although there are similarities between prognostic and aetiologic research, predicting outcomes does not focus on explaining their cause (14,621). Hence, this PhD study uses a simple longitudinal approach without following a cohort design to evaluate cause and effect (581). Prognostic modelling studies have been used in medicine to understand the course of health-related conditions, to examine specific risk factors in their association with prognosis, to develop and validate statistical models of risk and to help tailor treatment decisions to the individual patient (622,623). This information can be used when communicating information about disease and treatment to patients and families, to create clinical risk groups or as stratification models of disease severity (614). It is this latter use that is intended in this PhD study, identifying patient-reported variables that can be used to indicate deterioration in QOL and increase in palliative care needs.

Prognostic model building falls into two categories: predictive and explanatory models (617,624,625). Predictive models aim for providing good predictors with little consideration of

model structure or causal pathways among predictors (613). Model fit indices and prediction error are the main criteria for judging model adequacy (613). Explanatory models, however, are mainly concerned with hypothesis generation and with identifying the factors that predict a certain outcome without focusing just on which particular set of multiple variable produces the best model (614,619). The multivariable model that is built in this study for predicting deteriorating QOL falls into the latter category. This decision also relies on the fact that predictive models are often limited to data-dependent model building strategies only (626), with very little consideration of subject-matter knowledge. Statistical modelling in these contexts uses stepwise procedures for variable selection, whereby the choice of variables in the model is based on sequential hypothesis testing of individual predictors in an automated procedure (627). These procedures tend to yield overoptimistic models with too many variables included. This model of predictors for deteriorating QOL, however, is partly built from theory (330,357).

The second, often overlooked aspect of model building is the one of validating the model. Validation contains the two general aspects of accuracy (the degree to which prediction matches outcomes) and generalisability, the ability of the model to hold true in a different sample of patients (628,629). Validating the accuracy of a model entails the comparison of observed and predicted event rates for groups of patients (calibration), and distinguishing between future outcomes of a group of individuals (discrimination) (618,630). Both approaches rely on using the model in a new sample. This is problematic in multiple myeloma since follow-up until development of the outcome can take long. Mean survival time has increased in recent years (61,62). Therefore, in keeping with the data sources and the scope of the current study, internal validation and temporal validation procedures are used to validate the model, rather than validating it in a separate sample (614). Establishing generalisability of the set of predictors in a different population is a task for future research. Internal validation usually involves data-splitting into an exploratory and a confirmatory data set (631). Several ways of establishing these test and training sets have been proposed of which the most common way is to use a random sample. However, random splitting constitutes a weak procedure and tends to yield imprecise estimates (614,632). An alternative is temporal validation, evaluating the performance of a model on subsequent patients from the same centres (633). In this study, temporal validation is used by building the initial model on the combined datasets of the MyPOS validation study and the longitudinal PhD study, then validating it taking the temporal course of HRQOL in myeloma into account.

Different phases have been defined in prognostic research studies. The earliest conception of phases was proposed by Altman & Lyman (1998) (634). They distinguished three phases, exploratory studies that are hypothesis generating, exploratory studies that attempt to use an existing prognostic model to discriminate between patients at high and low risk of an outcome

(e.g. disease progression), and confirmatory studies attempting to validate a priori cut-off values on prognostic markers to define groups of high and low risk (634). This initial model was subsequently extended and reformulated in the guidelines for prognostic factor research published by the same research group (14). In this model, the authors distinguish between developmental studies, validation studies and impact studies. Developmental studies entail identification of important predictors within multivariable prognostic models with calibration and discrimination and internal validation techniques (635). Validation studies are studies that test the model's performance in new participants, usually comprising temporal validation and generalisability studies to discriminate groups of patients on the risk factors identified in the model (14,629). Impact studies finally use the prognostic model at the bed-side and try to quantify whether the model improves decision making and patient outcome in clinical practice (14). This PhD study only covers the developmental stage, with model identification and internal validation procedures, by building the model over three subsequent study phases – the systematic review and meta-analysis of factors associated with QOL in multiple myeloma (see section 2.2.2.3), the cross-sectional study (chapter 5), and the longitudinal survey (chapter 6). Further validation processes should entail a prospectively planned pooled analysis of individual patient data and eventually using the model in routine clinical practice for confirmatory and impact studies of its performance.

4.3.4 Phase 4: Longitudinal validity and reliability of the Myeloma Patient Outcome Scale for individual patient-monitoring

Research questions:

1. How does the MyPOS after its conversion to the format of its core module, the Integrated Patient Outcome Scale, perform psychometrically in terms of item quality, construct validity, and reliability?

2. Is the MyPOS reliable over time, both when measuring changes and stability in groups of patients and in individual patients?

3. Can the MyPOS validly reflect important changes in the individual multiple myeloma patient over time and can the minimally important difference both for patients that improved and for those that deteriorated be determined?

4. Is the MyPOS an acceptable instrument to monitor changes in symptoms and quality of life over time in multiple myeloma in the clinical setting?

Measurement is central to clinical practice, medical and health research. Measurement forms the basis for diagnosis, prognosis and evaluation of results of interventions. Especially in the context of palliative care and progressive disease, with its focus on whole-person care and patient-centredness, capturing the personal and social context of disease and including the wider factors impacting QOL is important. QOL measures are accepted as outcome measures in clinical research but less so in clinical practice (316). There are unique challenges when using QOL tools in clinical practice. These challenges concern: selecting appropriate measures, analysing data, providing feedback on scores to clinicians and patients, interpreting results and using results in clinical decision making (316,442,443). Rather than introducing the Myeloma Patient Outcome Scale in a wide-spread fashion in routine haematological practice, this PhD study focuses on establishing whether the MyPOS is suitable and of high enough quality for such an application.

In clinical research, the quality of inferences made in clinical trials is dependent on the soundness of the outcome measures used. Both the FDA and the EMA have specified minimum criteria for the psychometric quality of health outcomes scales (287,636,637), albeit only for application in clinical trials. The other two prominent sources for guidelines of instrument properties are the Scientific Advisory Committee of the Medical Outcomes Trust (638,639) and the COSMIN guidelines (640). All these sources differ slightly as to the attributes of measurement quality they define as essential. Central to all classifications are concepts of validity, usually split into the components content and face validity, construct validity and criterion validity, reliability, responsiveness (longitudinal validity), interpretability, and cultural and language adaptations (638-640). What is often lacking in these catalogues are explicit criteria for what constitutes good measurement. With the notable exception of Terwee et al. (2007) (641), no evaluative cut-off values are specified for different attributes. Moreover, Higginson and Carr (2001) (316) point out that these lists of measurement properties are geared towards an application in clinical research. Validation of outcome measures in clinical practice, however, necessitates an exploration of certain features that make a questionnaire easy to use in this context. Clinical utility entails features such as respondent burden, assessing floor and ceiling effects to evaluate whether the instrument is applicable in the target population, and responsiveness of scores for individual patients and not just groups of individuals (316,642).

Another feature of these guidelines is that they assume that the same set of quality criteria applies to all types of health outcome measures, a notion that Kirshner & Guyatt (1985) (643) refute by defining different purposes of measurement use in health care. The authors distinguish between discriminative, predictive and evaluative measures. Discriminative and predictive scales are used for screening and diagnostic purposes, usually to distinguish between individuals or groups and to identify those at risk for developing a certain outcome (643). Evaluative indices, on the other hand, are used to measure the longitudinal change in an individual or group. Kirshner & Guyatt

locate QOL measure within the latter category. Uniquely, they point towards the application of evaluative and predictive indices for the individual patient (and not solely for a group of patients), and it is in this context that screening and monitoring benefit clinical practice. Screening is the process of systematically searching for preclinical disease and classifying people according to their risk of presenting with a certain health problem or being at risk of experiencing a certain outcome (644). Screening programs usually relate to risk factors for chronic conditions. Within healthcare of cancer and chronic diseases, the early detection of recurrence of cancer (645,646) and emotional distress (647) usually constitute the largest screening applications. Similar to screening is the application of monitoring or surveillance, whereby repeated assessments of biological or health status parameters are used to track changes and patterns in key domains in a group of patients (648). Both applications of measurement work at the local level, i.e. in screening all newly diagnosed patients for emotional distress, or are used in the form of population monitoring as core epidemiological functions within public health (648).

When used for the individual patient, the question of accuracy and scientific quality of measures becomes paramount. However, as this application has not been popular within the field of health outcomes research, which has traditionally focused on comparing groups of patients on outcome measures within effectiveness research or for comparisons of health care delivery systems (283), a definition of what constitutes a set of necessary criteria for a health outcome measure to fulfil in order to be applied at the individual patient level is still lacking. The only work with an explicit focus on the evaluation of health status measures for purposes of individual patient-monitoring was published by McHorney & Tarlov in 1995 (649). They conducted a head-to-head comparison of five prominent QOL measures and specified measurement standards inclusive cut-off criteria that define the measure's suitability for individual monitoring. Essential are six criteria: (i) interpretability of scores, (ii) assessing the full range of underlying constructs across different age groups, diagnoses, severity and comorbidity, (iii) minimal floor and ceiling effects, (iv) reproducibility and minimal measurement error over time for individual patients, and (v) sensitivity to clinical change. The authors also recommend more stringent benchmarks for measurement errors to fit the longitudinal use of measures, thus asking for higher reliability or accuracy of scores, as high as 0.90 to 0.95 (649,650). Kirshner & Guyatt (1985) (643) defined similar criteria for psychometric properties applicable to evaluative measures. They emphasised the need for responsive measures that assess the construct of interest in sufficient gradations to register change (643). In addition to longitudinal construct validity, they also defined stable intra-subject variation as the second important criterion for evaluative measures.

Since there is no agreed framework for evaluating whether outcome measures are fit for the purpose of individual, longitudinal monitoring, it is proposed to use new psychometric methods to meet the more stringent criteria for reliability and responsiveness proposed by McHorney &

Tarlov (649). I suggest to use Generalizability theory, Rasch analysis and new methods for determining individual minimally important differences.

For establishing test-retest reliability of the measure the approach of Cranford et al. (2006) (651) will be followed. The authors used Generalizability theory (GT), an extension of classical test theory, to study dynamic change in emotional processes. Their approach developed in response to studying evolving emotional states and self-regulation via diary studies that require frequent self-reports of participants (652). Monitoring evolving concepts frequently poses challenges in its own right, usually due to respondent burden and the need to keep measures short (653). Brevity of measures results in psychometric challenges, particularly regarding reliability (654). This sacrifices redundancy which usually improves reliability, as well as sacrificing coverage of the full conceptual range of a construct of interest. Reliability in psychometric terms is formally defined as the ratio of signal variance to the total variance (655). Systematic change variation is often small compared to random measurement error variation and the reliability of change assessment hence becomes a question of detecting a small signal among high amounts of noise. Generalizability theory (656) offers an answer to that challenge by providing a much more fine-grained picture than just systematic variance and error/random variance (657). Within the GT approach, the variance of a set of scores is partitioned into its component parts and their interactions, along with an error component (658). Cronbach et al. (1972) (659) introduced the theory of generalizability to make it possible to assess multiple sources of measurement error. These error components consist of person variation (due to changes within the person), item variation and time variation. All possible interactions between these components are also explored (person by time variance, item by time variance, person by item variance and error) (658). Cranford et al. (2006) (651) then composed a set of four reliability indices using different combinations of these variance components to estimate various forms of reliability (for formulae see chapter 7). Via these four indices it is possible to judge the reliability of a measure on an average day, and to judge how well the measure discriminates between different persons on a given day. Finally, it is possible to assess how well a measure captures changes over time (651). Interpretation of these reliability indices follows the common guidelines (641). Different methods of assessing the reliability of within-person change have emerged in recent years (651,660), but Cranford and co-authors' method has been found to be the most applicable to the situation of assessing the reproducibility of the MyPOS for individual patient-monitoring. It is also the only approach that provides the estimation of how well a measure such as the MyPOS can discriminate between persons with different levels of the attributes/dimensions to be measured.

The reliability of the MyPOS is also assessed using the differential item functioning (DIF) approach first proposed by Hobart et al. (2009) (661). DIF analysis uses the Rasch measurement framework. In addition to Cranford's method, which offers an evaluation of the MyPOS as a

whole measure, Rasch analysis indicates reproducibility at the individual item levels and thus allows to satisfy the objective to assess which individual items are suitable for monitoring. The Rasch model was proposed by the Danish mathematician Georg Rasch in 1960 (662). Classical test theory confounds the performance of the scale with the measurement of people (661). In Rasch analysis, estimates of item and person parameters are separated which allows the assessment of quality of individual items that is not sample-dependent. One way of assessing the reproducibility of single items within the MyPOS is to conduct a DIF analysis. Via a two-way ANOVA of standardised residuals across the continuum of QOL and levels of QOL in the sample, the invariance of items can be quantified (661). There are two types of DIF which indicate different breaches of the principle of invariance. First, a significant time effect, also known as uniform DIF, shows that an item is not stable across time points. Second, non-uniform DIF (significant interaction between class intervals and time) indicates that there is general misfit of the item across the whole measurement continuum (661). Both uniform and non-uniform DIF will be assessed for all MyPOS items.

Classical test theory (CTT) and Rasch measurement are both measurement theories that underpin the psychometric evaluation of rating scales (663). Measurement theories describe how numbers on a rating scale relate to the constructs they seek to measure (663). CTT represents a relatively simple theory that posits that a person's score on a scale (the observed score) is the sum of the unobservable true score of that person on the trait that is measured (i.e. QOL or pain) and an associated measurement error (655,664). The major critique of CTT is its general weakness as a theory that cannot be tested (665). The parameters of the theory (the true score and the measurement error) cannot be determined in a way other than through the observable score and thus they cannot be evaluated for their accuracy (664,666). This leads to several problems, chief among them the problem that the assumptions of CTT are easily satisfied by datasets, even if they are not true (664,666). More pronounced is the problem that parameters cannot be determined with confidence and only ordinal raw scores can be analysed. Likert-type rating scales thus never generate interval measurement which has a direct negative effect on comparisons of scores between individuals and deriving meaning of a score for the individual per se. With ordinal scores, confidence intervals are too wide to allow this application (667). Moreover, all information in CTT on the validity and reliability of the scale pertains to the whole score and is sample-dependent. Thus, results obtained in samples of relatively well patients cannot be transferred to palliative care samples (316). One elegant solution that addresses these methodological problems is using latent trait theories such as the Rasch model. Rather than developing a model that best fits the data, the Rasch model defines measurement, so that data are fitted to the model to see if they meet the model's expectations (668). The Rasch model posits that an individual's response is a probability function only dependent on the difference between the

item location and the respondent location on a linear scale. Applied to health measurement scales this means that the response to an item is determined by (a) the QOL status of the person and (b) the level of health status impairment represented by the item. Questionnaires that meet the requirements of the Rasch model have interval scaling properties, meaning that patients are more likely to endorse items assessing less severe QOL problems (item difficulty or location) when they experience few symptoms and limitations that would negatively impact on their QOL (person ability).

Not only does the Rasch model allow an analysis of the individual items within the scale, its results are also sample-independent and show where along the measurement continuum the questionnaire is situated. Thus, more information than through simple analysis of floor and ceiling effects can be gained. The question can be answered whether the items fit the population which they target. In CTT analysis of scale targeting, floor and ceiling effects are considered to be present if more than 15% of respondents achieve the lowest or highest possible score (649). This indicates that items either asking about mild or severe/extreme levels of the construct are missing at either end of the scale. Floor or ceiling effects diminish the content validity of a scale and reduce reliability, since patients at the lower or upper level cannot be distinguished. This in turn affects responsiveness because changes cannot be measured at these ends of the spectrum (667). Within Rasch analysis, more information on the targeting of the scale is available. Fit statistics (mean location scores) for persons and items should be centering on zero (668), which indicates a well-targeted measure. In addition, a person-item location diagram which maps item locations to person locations allows an assessment whether the scale spans the entire range of person locations (thus all levels of QOL – from no problems/good QOL to severely impaired QOL) (512). A further technique within the Rasch framework is to use DIF (see reliability analysis above). DIF signals that different groups within the sample respond in a different manner to items. A consistent, systematic difference in the responses is called uniform DIF, which suggests splitting the item for these groups. If disease severity or phase of illness are variables producing DIF, then this could be an indication for a scale such as the MyPOS to work differently in these groups (668).

The shift in focus and the growing interest in using QOL results at the individual patient-level is especially driven by the need to track changes in QOL and symptoms over time (432,454,669). Responsiveness analysis use QOL data that was assessed repeatedly over time and can thus make use of the time course and differences in QOL scores from time point to time point (650). However, results usually apply to a group of patients. The sensitivity of change or responsiveness to change of individual scores has received less attention in the methodological literature (641). In these analyses, what might constitute a meaningful change for an individual certainly differs from statistical changes. Jaeschke et al. (1989) (670) defined the minimally important difference (MID)

as the indicator of meaningful change as “the smallest difference in score in the domain of interest which patients perceive as beneficial and which would mandate, in the absence of troublesome side effects or excessive costs, a change in patient management” (p.408). Reviews have defined methods to assess this MID in HRQOL, mainly splitting approaches into anchor-based and distribution-based methods (671,672). Distribution-based methods rely on effect sizes (673-675), the standard error of measurement (676,677), the responsiveness index (678) and the reliable change index (679). Distribution-based approaches usually represent statistically rather than clinically significant change. Anchor-based approaches use an external criterion to determine the significance of change in global QOL or well-being, usually a global change rating that is completed by the patient (680). Alternatively, significant clinical events (e.g. laboratory or physiological measures, treatment benefit) or ratings by clinicians are used (650). A review of possible approaches is presented in Crosby et al. (2003) (672).

Methodological challenges concerning determining clinically relevant change centre around a variety of methods being proposed with an overall lack of consensus regarding definitions and methodological approaches (672,681). Furthermore, the MID can be determined at the group or individual level (682). This is determined by the anchor. However, this distinction is often not taken into account (683). Moreover, the interpretation of MID values at the individual level is accompanied by uncertainties. MID values at the individual level are immensely influenced by scale reliability and measurement precision (684). Although this is a well-known fact and QOL questionnaire are subject to lower reliability values due to their multidimensionality (672), oftentimes the same thresholds for relevant changes are proposed for individual-level as for group-level applications (685,686). Vet and co-authors (2010) (683) have proposed a way to visualise the uncertainty around MID values, not just using a 95% confidence interval but evaluating whether the MID value exceeds the measurement error. Thus, thresholds of statistical significance are brought together with thresholds of clinical significance (687). The Amsterdam group used this approach to compare MIDs on the EORTC QLQ-C30, showing that at least moderate to large changes derived from distribution-based methods need to be defined in order to measure change reliably at the individual patient level (683,688). For the evaluation of responsiveness of the MyPOS subscales, methods to determine responsiveness at the individual patient-level and methods of displaying uncertainty and confidence intervals around these MIDs pioneered by Vet et al. (2010) (683) are used.

Finally, information from phase 3 will be integrated with the results from phase 4 of this analysis. In phase 1 and 2, the cross-sectional and longitudinal analysis, data sets of variables potentially influencing QOL are collected. In a series of regression models, a prognostic model of variables related to poor or deteriorating QOL identified. The psychometric perspective in phase 4 complements this modelling approach by identifying targets for longitudinal monitoring in

multiple myeloma from a measurement perspective. Both analyses try to answer the same question, but use different approaches to help identify targets for screening and monitoring in myeloma.

4.4 History of the study and development of the MyPOS

This longitudinal study on quality of life in multiple myeloma represents the last phase in a programme of research started at the Cicely Saunders Institute at King's College London in 2010. Prior to this year, Myeloma UK, the largest patient-led charity for multiple myeloma operating in England and Scotland, had announced to fund a five-year research programme to improve the wellbeing of myeloma sufferers, with the aim to directly inform the healthcare policy-making process and leading to improvements in the clinical care of patients. They were particularly interested to understand which factors impact on QOL and wanted to fund the development and validation of myeloma-specific instruments to assess QOL in clinical practice. The Cicely Saunders Institute offered special expertise in the development of measures in populations in which outcome measurement can be a challenge due to their advanced disease stage. The Support Team Assessment Schedule (STAS) and the Palliative care Outcome Scale (POS) were among the first outcome measures to be developed for palliative care (689). Many versions for different conditions (multiple sclerosis, dementia, renal disease etc.) are now available, with a considerable number of culturally adapted and translated versions (for example the APCA African POS (689)). The newest iteration is the Integrated Palliative Care Outcome Scale (IPOS) (819), which integrates 15 years of work in the development of the POS measure and represents a refined patient- and proxy (staff-reported) version of the POS.

The first step in the Myeloma-UK funded research project was a systematic literature review (359) to identify instruments that were developed and validated for use in patients with myeloma. Subsequently, two more questionnaires were published, the Functional Assessment of Cancer Therapy – Multiple Myeloma (FACT-MM) (513), which is in its initial development phase, and the M.D. Anderson Symptom Inventory – Multiple Myeloma (MDASI-MM) (690). The review identified no tool specifically developed for clinical use (359). Subsequently, a qualitative study explored the meaning of QOL in this group and also explored participants' views on existing QOL tools, their utility, breadth of coverage of the construct and views on their acceptability (357). A theoretical model of quality of life in multiple myeloma was derived from that data. These findings were used to develop a prototype version of the Myeloma Patient Outcome Scale (MyPOS). Since developing a new tool in the presence of existing instruments to measure a construct in a patient group needs to be well-argued, it was decided to modify an existing questionnaire and thus harness the existing development work and field-testing of items. It was

decided to adapt the Palliative Care Outcome Scale (POS) since this was the only tool that was initially developed with a specific focus on use in clinical care and its scaling considered the impact of symptoms and problems rather than the status of these problems (512). The POS also offered items that had been designed specifically for a more advanced population, a feature that the new tool for clinical use in myeloma needed to have. Items for the prototype version were derived from the qualitative work, the theoretical model of QOL in myeloma, and existing questionnaires identified in the systematic review (357). The initial 33-item version, using a combination of structured and open items (with 10 items taken from the POS and 23 newly written items), was pre-tested in cognitive interviews with twelve participants. The refinement was conducted in two stages, with a first rewording of questions being undertaken after an initial round of six interviews and further six interviews, after which 2 items were removed because of redundancy. The formatting was also changed (384).

The 27-item version of the MyPOS was then tested for validity and reliability in a multi-centre sample of 380 patients. Results of these analyses, combined with further results from the longitudinal validation study, are shown in Table 6. In this table, the MyPOS is further compared to the other two most prominent disease-specific HRQOL tools, the EORTC QLQ-MY20 (221,310) and the MDASI-MM (690). Structural validity testing of the MyPOS yielded three subscales, Symptoms & Function, Emotional Response and Healthcare Support. Construct validity was further tested using hypothesis testing/subgroup comparisons and convergent/discriminant validity comparison to other measures. MyPOS scores behaved as hypothesised with higher scores (worse QOL) in those with active disease, those receiving chemotherapy and those with a poorer ECOG performance status. Reliability testing was confined to assessment of internal consistency which was high (alpha = 0.89), given that the MyPOS is a multi-dimensional, clinical measure.

After the initial validation and before the set-up and application to the ethics committee had been completed for the longitudinal survey, the Palliative care Outcome Scale was transformed to the Integrated Palliative care Outcome Scale (IPOS). This measure builds on 15 years of development work of the POS and its extensions. It combines the most important elements of the original 10-item palliative care measure with a symptom list stemming from the POS-S symptom measure (819). Further cognitive interviewing work from the development of the African POS (689) regarding item and response option wording was also incorporated. The IPOS has undergone psychometric testing including cognitive interviewing in phase 1, to assess content/face validity and acceptability (818), and full construct validity as well as test-rest and inter-rater reliability assessment (819). To aid the harmonisation of the different measures of the POS family, it was subsequently decided to adapt all disease- and condition-specific measures of

Table 6: Comparison of the main myeloma-specific quality of life and symptom questionnaire

Measurement domain	Myeloma Patient Outcome Scale (384)	EORTC QLQ-MY20 (221,310)	M. D. Anderson Symptom Inventory – Multiple myeloma (690)
No of items	33	50	26
Content validity	Based on existing questionnaires and over 70 qualitative interviews with MM patients with different disease stages for item generation, cognitive testing with 12 MM patients	Literature search and informal interviews with oncologists, haematologists and patients for item generation, cognitive testing with MM patients	Literature search and informal interviews with clinicians and researchers for item generation, cognitive testing with 20 MM
Construct validity			
Structural validity	Initial exploratory factor analysis found three subscales, subsequent confirmatory factor analysis confirmed subscale structure	Multi-trait scaling analysis, no factor analysis	–
Convergent/ discriminant validity	High correlations with QLQ-C30 global QOL scale, and with physical, role, cognitive, social function and MY-20 disease symptoms and side effects. MyPOS Emotional subscale correlated highly with QLQ-C30 emotional function and QLQ-MY20 future perspectives. No correlation between MyPOS Healthcare support and any subscale on the EORTC.	Moderate correlations between global QOL scale on QLQ-C30 with all items on QLQ-MY24, except for social functioning	Moderate to strong correlations of MDASI severity subscale with QLQ-C30 subscales; activity-related interference subscale strong correlation to physical function subscale on the QLQ-C30, MDASI symptom subscales correlated well with QLQ-MY20 disease symptoms and side effects
Subgroup comparisons/ Hypothesis testing	MyPOS total scores higher (worse QOL) in those with newly diagnosed or relapsed versus stable disease MyPOS total scores higher in those receiving chemotherapy versus those not on treatment MyPOS Symptoms and Function subscale higher in those with low performance status.	Improvement in disease symptoms subscale in those responding to treatment versus non-responders Poor performance status at baseline associated with disease symptoms, side effects and body image subscales	Patients with good performance status significantly lower MDASI-MM subscales, also on MM-specific symptom items, large effect sizes for differences (≥0.7)
Reliability			
Internal consistency	Cronbach's alpha 0.89	Cronbach's alpha 0.92	Cronbach's alpha 0.85 – 0.91
Test-retest reliability	Excellent test-retest reliability (>0.90) and moderate to good reliability for screening and monitoring (results from this PhD study)	–	–

Measurement domain	Myeloma Patient Outcome Scale (384)	EORTC QLQ-MY20 (221,310)	M. D. Anderson Symptom Inventory – Multiple myeloma (690)
Responsiveness	Moderate to strong correlation to external change question, reliable identification of those that improved, remained stable or deteriorated with misclassification only in case of deterioration (results from this PhD study)	Improvement over time in subscales disease symptoms and future perspectives with bortezomib treatment Significant decreases over time in disease symptoms, side effects and body image subscales in those achieving at least a partial response	Difference scores between patients whose ECOG performance status worsened and those with stable/improved performance status were significant for each MDASI-MM subscale Increases in all subscales and some single items 7 days post stem cell transplantation
Minimal important difference (MID)	Total score: MID of 2.5 for improvement and 4.5 for deterioration; MIDs for all subscales (results from this PhD study)	–	–
Floor/ceiling effects	Floor effects for nausea, vomiting, diarrhoea, poor appetite, sore/dry mouth, drowsiness, tingling in hands and feet and Healthcare support subscale (results from this PhD study)	Some items skewed but full range of responses Healthcare support scale (4 items) removed due to ceiling effects	–
Acceptability	Acceptability and burden from patient interviews Mean time to complete 7 minutes Percentage of missing items minimal overall Good acceptability of monitoring	–	–

the POS to the new IPOS format, with disease-specific items being listed in a modular approach after the core-IPOS items. Thus, the MyPOS was adapted to the new IPOS format. The changes are detailed in Figures 9 and 10. Figure 9 reproduces the original MyPOS version that was used in the initial validation study (384), Figure 10 details the changes that were made to adapt the MyPOS to the general IPOS format. These changes were as follows:

- Item 2, a-l (original version): This symptom list was extended by two symptoms, Poor appetite and Drowsiness, that are incorporated in the symptom list of the IPOS. Furthermore, the symptom list was reordered to fit the general ordering of symptoms in the IPOS. The MyPOS original item “Fatigue or lack of energy” was reworded to “Weakness or lack of energy” as in the IPOS symptom list, as was the original MyPOS item “Mouth problems” to “Sore or dry mouth”. Both changes were made following

results from cognitive interviewing regarding the use of technical jargon or the ambiguity of the item phrasing (818). The symptom list now contains all the symptoms contained in the original IPOS and two further myeloma-specific symptoms, Tingling in the hands/feet and Difficulty remembering things, two symptoms that were mentioned as important by patients in the qualitative and development work to the original MyPOS (357,384).

- Page 2 of the new MyPOS contains all generic IPOS items. Three of these seven items, Patient anxiety, Depression and Information needs, had already been part of the original MyPOS and were thus moved from their original place to the newly formed second page. The four items Family anxiety, Feeling at peace, Sharing feelings with family/friends and Practical matters are items from the IPOS. The ordering of items follows the order in the IPOS (819).

- All myeloma-specific items contained within the original MyPOS were moved to a third page. These items consist of the specific impact of myeloma on activities & participation, emotional well-being and of questions regarding the quality of care. No further changes to the item wording or response options were made for these items.

All data collection in the longitudinal survey regarding palliative care concerns and myeloma-specific quality of life was performed using the new, adapted version of the MyPOS.

Figure 9: The original version of the Myeloma Patient Outcome Scale (MyPOS) before it was adapted to the IPOS format. All questions are preceded by "Over the past week…".

1	What are your main problems or concerns at the moment?	[Open question with three empty boxes for respondent to complete, numbered 1-3]				
2	Below is a list of symptoms, which you may or may not have experienced. For each symptom please tick one box that best describes how it has affected you over the past week:	Not at all	Slightly	Moderately	Severely	Over-whelmingly
a	Pain	I have not had this symptom in the past week	Little or no effect on activities or concen-tration	Some effect on activities or concen-tration	Marked effect on activities or concen-tration	Unable to think of anything else
b	Fatigue or lack of energy					
c	Shortness of breath					
d	Diarrhoea					
e	Constipation					
f	Nausea (feeling like you are going to be sick)					
g	Vomiting (being sick)					
h	Mouth problems					
i	Poor mobility					
j	Tingling in the hands and / or feet					
k	Difficulty remembering things					
l	Please list any other symptoms not mentioned above, and tick one box to show how they have affected you over the past week:	[Three boxes beneath symptoms list for respondent to add additional symptoms, numbered 1-3]				
3	Have you been able to carry out your usual activities without help from others?	Yes, as much as I wanted	Most of the time	Sometimes	Occasionally	No, not at all
4	Have you been able to pursue your hobbies and leisure activities?					
5	Have you been able to spend quality time with family and friends?					
6	Have you been worrying about your sex life?	No, not at all	Occasionally	Sometimes	Most of the time	Yes, always
7	Have you been feeling depressed?					
8	Have you been feeling anxious or worried about your illness or treatment?					
9	Have you been worrying about infections?					
10	Have you been worrying about your physical appearance?					
11	Have you been worrying about your financial situation?					
12	Have you been worrying that your illness will get worse?					
13	Have you felt able to cope with your illness and treatment?	Yes, always	Most of the time	Sometimes	Occasionally	No, not at all
14	Are you able to contact your doctors or nurses for advice if needed?					
15	Do your doctors and nurses show a good standard of knowledge skill when treating you?					
16	Do your doctors and nurses show care and respect when treating you?					
17	Do you have enough information about your illness and treatment?	Enough Information	Information received	Information received	Very little information	No information received
18	Do you have enough information about what might happen to you in the future?	the right amount for me	but hard to understand	but would like more	and would like more	and would like information

Figure 10: The modified version of the MyPOS after adaptation to the IPOS format.

1	What are your main problems or concerns at the moment?	[Open question with three empty boxes for respondent to complete, numbered 1-3]				
2	Below is a list of symptoms, which you may or may not have experienced. For each symptom please tick one box that best describes how it has affected you over the past week:					
a	Pain	Not at all	Slightly	Moderately	Severely	Over-whelming-ly
b	Shortness of breath					
c	***Weakness*** or lack of energy					
d	Nausea (feeling like you are going to be sick)					
e	Vomiting (being sick)					
f	**Poor appetite**					
g	Constipation					
h	***Sore or dry mouth***					
i	**Drowsiness**					
j	Poor mobility					
k	Diarrhoea					
l	Tingling in the hands and / or feet					
m	Difficulty remembering things					
n	Please list any other symptoms not mentioned above, and tick one box	[Three boxes beneath symptoms list for respondent to add additional symptoms, numbered 1-3]				
3	***Have you been feeling anxious or worried about your illness or treatment?***	No, not at all	Occasionally	Sometimes	Most of the time	Yes, always
4	**Over the past week, have any of your family or friends been anxious or worried about you?**					
5	***Have you been feeling depressed?***					
6	**Have you felt at peace?**					
7	**Have you been able to share how you are feeling with your family or friends?**					
8	***Have you had as much information as you wanted?***					
9	**Have any practical matters resulting from your illness been addressed? (such as financial or personal)**	No pro-blems	Problems being addressed	Problems partly addressed	Problems hardly addressed	Problems not addressed
10	Have you been able to carry out your usual activities without help from others?	Yes, as much as I wanted	Most of the time	Sometimes	Occasio-nally	No, not at all
11	Have you been able to pursue your hobbies and leisure activities?					
12	Have you been able to spend quality time with family and friends?					
13	Have you been worrying about your sex life? Have you been worrying about infections	We would like you to answer this question whether or not you are sexually active. If you would prefer not to answer please tick here:				
14	Have you been worrying about your physical appearance?	No, not at all	Occasionally	Sometimes	Most of the time	Yes, always
15	Have you been worrying about your financial situation?					
16	Have you been worrying that your illness will get worse?					
18	Have you felt able to cope with your illness and treatment?					
19	Are you able to contact your doctors or nurses for advice if needed?					
20	Do your doctors and nurses show a good standard of knowledge skill when treating you?	Yes, always	Most of the time	Sometimes	Occasionall y	No, not at all
21	Do your doctors and nurses show care and respect when treating you?					
22	Do you have enough information about your illness and treatment?					

Reordering and extension by general IPOS symptoms

Response options – impact on activity or concentration deleted

Bolded items are new items from IPOS
Bolded items in italics are IPOS items that had already been part of the original MyPOS. These were moved to the second page.

Remaining original MyPOS items were moved to a third page.

I was the research assistant on the MyPOS project and took part in the systematic review work, the qualitative study and the development and validation of the MyPOS. I worked on recruitment of participants, conducting data collection, analysing data and publication of the research findings. The dataset from the multi-centre MyPOS validation study was used in the secondary analysis of this PhD research study, forming a part of phase 1, cross-sectional analysis of symptom burden and quality of life in multiple myeloma and initial modelling of predictors for poor quality of life in this patient group. The validation study of the MyPOS was cross-sectional in nature and precluded the assessment of longitudinal validity (sensitivity to change/responsiveness analysis with derivation of the MID) and reliability (test-retest reliability in particular). To achieve full clinical utility (316) of the instrument, it was necessary to recruit a clinically representative sample to study measurement characteristics over time. Also, there was a need to understand and improve the illness experience of people with myeloma throughout the whole disease trajectory, into stable phases and after relapsed/during refractory disease. To date, as shown in section 2.2.2.2, only a handful of studies have measured HRQOL at several points in time, usually before, during and post-treatment. Large, naturalistic studies are missing (95). The need for a longitudinal study that would identify predictors for poor HRQOL and could therefore help to prognosticate when prominent problems in different domains of HRQOL would make the involvement of palliative care beneficial to these haematological cancer patients, was also identified by St. Christopher's Hospice London. They funded this PhD study from May 2011 onwards, using a grant endowed by a former patient with multiple myeloma for the improvement of QOL in this condition. I developed the application to the funder, together with the chief investigator Irene J. Higginson and the Quality of Life in Multiple Myeloma group at the Cicely Saunders Institute, consisting of Dr. Richard Siegert (psychometrics and statistical lead, replaced by Dr. Gao Wei, the second supervisor of this PhD study after Dr Siegert changed post in 2012), Dr Steve Schey (clinical lead for haematology) and Dr Polly Edmonds (clinical lead for palliative care). I developed and lead the application for ethical and local approval in the participating NIHR/NHS trusts. I also recruited participants for the first phase, piloting of methods, of the longitudinal study. The recruitment for the longitudinal survey was completed by the research nurses in all participating centres, with the exception of recruitment taking place at King's College Hospital and Guy's Hospital, London, two trusts in which this tasks was shared between two research nurses and me. Prior to recruitment, I held a training session for each participating site to train study-site staff in the standard operating procedures for this study. Once participants had completed and returned their first questionnaire, I performed follow-up contact via letter and phone calls and subsequent data collection. Data entry, data analysis and interpretation as well as publication was also performed and led by me. As part of the dissemination of findings to a wider audience, a successful conference was run on 31st March 2016 at the Cicely Saunders Institute. Results from this PhD study, together with overall results of the research programme and other

talks focusing on routine monitoring of outcomes in this patient group, were presented to an audience of clinicians (both from the fields of haematology and palliative care), researchers and students and patients and their families. Further dissemination involved international conferences and dissemination through patient-led charities like Myeloma UK (for a list of publications, talks and poster presentation see section "Publications, presentations and other output", page 10).

4.5 Ethical issues

4.5.1 Ethical approvals

The cross-sectional dataset used in secondary analysis was derived from the validation study of the Myeloma Patient Outcome Scale. Research Ethics Committee approval was granted by the South East London REC-3 (REC reference number 10/H0808/133). Local research governance approvals were obtained for all participating sites taking part in this multicenter study. These were Bradford Teaching Hospitals NHS Foundation Trust, Colchester Hospital University NHS Foundation Trust, Epsom and St Helier University Hospitals NHS Trust, Guy's and St Thomas' NHS Foundation Trust, King's College Hospital NHS Foundation Trust, Maidstone and Tunbridge Wells NHS Trust, Mid Yorkshire Hospitals NHS Trust, Northampton General Hospital NHS Trust, Pennine Acute Hospitals NHS Trust, St Christopher's Hospice London, Surrey and Sussex Healthcare NHS Trust, University Hospital Coventry and Warwickshire NHS Trust, Weston Area Health NHS Trust, and Wye Valley NHS Trust. All patients were screened by a member of their clinical team before being approached. Written informed consent was obtained from every participant. Data collection was voluntary and took part at a time and place convenient to the participant. Completed questionnaires were screened for issues needing immediate clinical attention and, if necessary, consent was thought from participants to alert their primary clinical team to these issues (distress protocol).

The longitudinal, multicenter study involving patients with multiple myeloma and their informal carergivers was approved by the Central London Ethics Committee (REC reference number 13/LO/1140). Site-specific local approvals were received from Bradford Teaching Hospitals NHS Foundation Trust, Burton Hospitals NHS Foundation Trust, Colchester Hospital University NHS Foundation Trust, East Cheshire NHS Trust, Epsom and St Helier University Hospitals NHS Trust, Guy's and St Thomas' NHS Foundation Trust, King's College Hospital NHS Foundation Trust, Medway NHS Foundation Trust, Mid Yorkshire Hospitals NHS Trust, Royal Free London NHS Foundation Trust, Surrey and Sussex Healthcare NHS Trust, and University Hospital Coventry and Warwickshire NHS Trust. The study received approval for adoption onto the National Institute for Health Research Clinical Research Network (NIHR CRN) Portfolio.

Sponsorship of the project was provided by King's College London and King's College Hospital NHS Foundation Trust. A minor amendment for change in questionnaire booklet layout was approved by the ethics committee in April 2014. The correspondence with the ethics committee, amendment and approvals are included in Appendix A.

4.5.2 Ethical considerations

Ethical considerations are detailed in the study protocol for ethics, available in Appendix B. A detailed discussion of the ethical issues around longitudinal survey research in palliative care was prepared for the application to the research ethics committee. This discussion is provided in Appendix C, Ethical considerations in survey research.

5 Results: The impact of symptoms and palliative care concerns on health-related quality of life in multiple myeloma: a multi-centre study

In this chapter, I present the results of the cross-sectional, secondary analysis of symptom burden and factors associated with health-related quality of life in multiple myeloma. The objectives of this study were:

(a) To determine the prevalence and severity of common symptoms and problems in patients with multiple myeloma at various stages of their disease, specifically for those with relapsed or progressive disease.

(b) To determine whether patients in the advanced stages of myeloma experience a different symptom and problem profile than patients in earlier stages

(c) To determine which demographic and disease characteristics were associated with a lower quality of life and more symptoms and problems, testing the hypothesis whether general symptom level and specific symptoms had a stronger influence on HRQOL than disease characteristics

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The impact of disease-related symptoms and palliative care concerns on health-related quality of life in multiple myeloma: a multi-centre study

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Abstract

Background: Multiple myeloma, the second most common haematological cancer, remains incurable. Its incidence is rising due to population ageing. Despite the impact of the disease and its treatment, not much is known on who is most in need of supportive and palliative care.
This study aimed to (a) assess symptom severity, palliative care concerns and health-related quality of life (HRQOL) in patients with multiple myeloma, and (b) to determine which factors are associated with a lower quality of life. We further wanted to know (c) whether general symptom level has a stronger influence on HRQOL than disease characteristics.

Methods: This multi-centre cross-sectional study sampled two cohorts of patients with multiple myeloma from 18 haematological cancer centres in the UK. The Myeloma Patient Outcome Scale (MyPOS) was used to measure symptoms and concerns. Measures of quality of life included the EORTC QLQ-C30, its myeloma module and the EuroQoL EQ-5D. Data were collected on socio-demographic, disease and treatment characteristics and phase of illness. Point prevalence of symptoms and concerns was determined. Multiple regression models quantified relationships between independent factors and the MyPOS, EORTC global quality of life item and EQ5D Index.

Results: Five-hundred-fifty-seven patients, on average 3.5 years (SD: 3.4) post-diagnosis, were recruited. 18.2 % had newly diagnosed disease, 47.9 % were in a treatment-free interval and 32.7 % had relapsed/progressive disease phase. Patients reported a mean of 7.2 symptoms (SD: 3.3) out of 15 potential symptoms. The most common symptoms were pain (72 %), fatigue (88 %) and breathlessness (61 %). Those with relapsed/progressive disease reported the highest mean number of symptoms and the highest overall palliative care concerns ($F = 9.56$, $p < 0.001$). Factors associated with high palliative care concerns were a general high symptom level, presence of pain, anxiety, low physical function, younger age, and being in the advanced stages of disease.

Conclusion: Patients with multiple myeloma have a high symptom burden and low HRQOL, in the advanced and the earlier stages of disease. Identification of patients in need of supportive care should focus on assessing patient-reported outcomes such as symptoms and functioning regularly in clinical practice, complementary to traditional biomedical markers.

Keywords: Multiple myeloma, Health-related quality of life, Palliative Care Outcome Scale, Symptom burden, Quality of life, Palliative care

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Background

Haematological malignancies belong to the most common cancers worldwide [1]. Multiple myeloma is the second most common haematological malignancy with an incidence of 3.29 to 4.82 per 100,000 individuals per year worldwide [2]. Multiple myeloma is characterised by a specific pattern of end-organ damage with destruction of the bones, bone marrow failure and renal failure. With the introduction of novel therapies and autologous stem-cell transplantation survival has been extended, especially for patients younger than 60 years [3]. However, since multiple myeloma remains an incurable disease, life expectancy is limited. 40.3 and 20.5 % of patients survive 5 and 10 years, respectively [3, 4]. Despite improvements in therapies, patients face progressive disease, interspersed with intervals of stable disease with minimal or maintenance treatment [5]. Symptoms may persist into treatment-free intervals [6], added onto which treatment-related toxicity further impacts on health-related quality of life (HRQOL) [7, 8].

There is evidence that myeloma patients suffer more symptoms and problems than other haematological cancers. A study from Denmark reported a mean symptom level of 5.6 symptoms with 2.3 symptoms identified as severe [9]. Myeloma patients reported the highest level of pain, fatigue and constipation, alongside problems with physical, role, and social function [9, 10]. A study from the Eindhoven cancer registry including myeloma patients up to 10 years post-diagnosis and comparing results with an age- and gender-matched normative population, found similarly diminished and clinically relevant compromises in all functioning subscale scores of the EORTC QLQ-C30 questionnaire [11]. Again, symptoms of pain, fatigue, but also breathlessness, nausea and vomiting and peripheral neuropathy were reported by patients to be the most bothersome symptoms [11]. The general high symptom level and the importance of high symptom burden in conjecture with mental health symptoms were identified as strong determinants of health-related quality of life (HRQOL) in a recent study enrolling myeloma outpatients in a multi-centre, cross-sectional study [12].

Longitudinal observational evidence of how HRQOL changes over the disease course focuses entirely on stem cell transplantation populations. Here, results mainly support the fact that myeloma patients experience a high symptom burden even before stem cell collection, as shown in a study with 94 patients receiving high dose melphalan and autologous stem cell transplantation, reporting at least moderate fatigue, pain, anxiety and depression at baseline [13]. After transplantation most symptoms improved, but depression and overall quality of life deteriorated. That recovery to full functioning and symptom levels prior to therapy is often not possible for patients with myeloma was demonstrated by a cross-sectional postal survey of 650 patients at different disease stages [6]. Recovery during subsequent treatment-free intervals was often not fully achieved and patients lived with a profound impact of the disease, its disease-related symptoms but also treatment-related toxicities [6].

Thus, the disease is an example of the changing face of cancer with patients experiencing a chronic disease trajectory [14] during which a variety of symptoms, psychological and social factors impact on patients' quality of life. However, the aspect of quality of life is still underrepresented in myeloma research, both as an outcome in evaluation of cancer treatment and in impacting treatment and supportive care guidelines [15, 16]. Descriptive studies of HRQOL are mainly cross-sectional in nature and focus on treatment or trial populations that receive autologous stem cell transplantation [17–22]. However, information on patients in later treatment phases is mainly lacking. Only one study by Boland and co-authors enrolled patients at a median of 5.5 years post diagnosis, including patients in later treatment intervals [23]. Thus, relatively little is known about how HRQOL and physical and psychosocial symptoms change over time and in the advanced stages of disease. This information would be vital to understand when patients experience periods in the disease trajectory during which they would benefit from additional support. This would help target services to those individuals most at risk, who could then benefit from early and preventive supportive care interventions. Further, the role of general symptom level and other disease- and treatment-related determinants in their influence on HRQOL remains conflicting [12, 16]. In focusing on the advanced stages of myeloma, existing and commonly used questionnaires such as the EORTC QLQ-C30 might underrepresent some of the problems and concerns regarding information and service provision that are of particular interest to myeloma patients [24]. We therefore wanted to focus on further problems and concerns that are important to patients with multiple myeloma, in addition to symptom burden, and to understand how symptom burden and problems differ during different treatment phases.

In this study we sought to determine the prevalence and severity of common symptoms and problems in patients with multiple myeloma at various stages of their disease, specifically for those with relapsed or progressive disease; and to determine whether patients in the advanced stages of myeloma experience a different symptom and problem profile than patients in earlier stages. We also sought to determine which demographic and disease characteristics were associated with a lower quality of life and more symptoms and problems, testing the hypothesis whether

general symptom level and specific symptoms had a stronger influence on HRQOL than disease characteristics.

Methods

Study design and participants

For this multisite, cross-sectional study patients with multiple myeloma were recruited from both inpatient stem cell transplantation units and outpatient haematology clinics in 18 centres in the United Kingdom. Participating hospitals included a mixture of tertiary transplant centres and district general hospitals to ensure a representative sample of patients from different settings. The analysis for this study consists of two cohorts of patients that were recruited 1 year apart (cohort 1 was recruited from February 2013 to August 2013 and cohort 2 was recruited from April 2014 to September 2014) – one cohort for validating a new questionnaire to measure disease-specific quality of life in multiple myeloma (the Myeloma Patient Outcome Scale, MyPOS) ($n = 380$ myeloma patients) and one cohort for a longitudinal study, determining the impact of physical and mental symptoms on quality of life, and enrolling patients with multiple myeloma that were either newly diagnosed or had received treatment before ($n = 235$ myeloma patients).

Inclusion criteria for both studies were: age ≥18 years, confirmed diagnosis of multiple myeloma that had been disclosed to the patient, and the capacity to give informed written consent. Exclusion criteria were: Patients who were too unwell, distressed or symptomatic to participate as judged by their clinical team, patients with severe neutropenia or for whom myeloma was not the most important health problem.

Procedures

Consecutive patients were screened by a member of the clinical team for eligibility before being approached by clinicians in the clinic or on the ward. If they signalled interest they then met with a research nurse who explained the study and obtained written consent. All were informed that participation was voluntary and would not affect the medical management in any way. At this point the research nurse also completed the demographic information with the participant. The patient-reported questionnaires were completed by patients in paper format either during their clinic visit or at home. In case of completion at home, patients were supplied a pre-paid envelope for returning the questionnaires to the institute. Information on patients' medical history and the treatments they had received was extracted from the medical notes by the clinicians or research nurses with the permission of the patient. All non-participants (those who were ineligible and those who declined) were asked for consent to record limited demographic and treatment details in order to compare these against the study sample.

Data collection and measures

Patient-reported outcome variables

The two main outcomes of the study, quality of life and symptom burden/palliative care concerns, were assessed using two generic and two disease-specific questionnaires. Choice of patient-reported outcomes was based on a systematic review of HRQOL validated in multiple myeloma [25]. Generic quality of life was measured with the European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire QLQ-C30 (version 3) [26] and the EuroQOL 5D-3L questionnaire [27]. One myeloma-specific quality of life questionnaire, the EORTC QLQ-MY20 [28, 29], was used to reflect disease-specific symptoms and concerns. Both the generic and the disease-specific version of the EORTC were chosen as they have undergone the most extensive psychometric validation in myeloma patients [25], are considered to be the gold standard in clinical trials [15] and therefore give a valid account of HRQOL in multiple myeloma. Scores from the EORTC QLQ-C30 were linearly transformed and subscales were formed according to the published guidelines [30]. For the myeloma module QLQ-MY20, the two symptom subscales and two functional subscales were formed according to the guidelines published in the initial validation study [28, 29]. For the EuroQOL 5D-3L questionnaire, the US norms were used to convert the health states into the single summary index [27].

The Myeloma Patient Outcome Scale (MyPOS) [31] formed the main outcome for determining point prevalence of disease- and treatment-related symptoms and to measure palliative care concerns, such asconcerns regarding functional ability in daily life, feeling at peace, concerns regarding the future and fear of dying, information needs and concerns regarding practical matters and financial burden of disease (for all items in the questionnaire see Additional file 1: Figure S1). Palliative care concerns in this context focus on the outcomes that reflect the specific goals of palliative care, namely to promote an individual's quality of life and to relieve any distressing symptoms and to offer emotional, spiritual and psychological support [32]. The MyPOS therefore focuses on assessing those areas that are key domains for patients experiencing a higher disease burden. The MyPOS is the only available questionnaire that assesses outcomes important to palliative care in late stage and earlier but symptomatic disease across settings [32]. The generic and disease-specific outcome measures in their combination allow to determine which myeloma patients experience a high burden, either through a high symptom level, high burden from specific symptoms or from wider psychological, spiritual or practical concerns.

The presence of clinically relevant anxiety or depression was measured using the Hospital Anxiety and Depression Scale (HADS) [33], both of which are common problems in cancer patients and might be important problems associated with burden and HRQOL. The Hospital Anxiety and Depression Scale is a validated self-report questionnaire consisting of 14 items, seven items each assessing depression or anxiety with the two subscale scores ranging from 0 to 21. A cut-off point of 8 out of 21 per subscale is used to define clinical cases of depression or anxiety, respectively, and higher scores indicate higher depression or anxiety [34].

Table 1 presents a short description of each outcome measure and its scoring procedure.

Sociodemographic and clinical information assessed via patient interview

Demographic information on age, gender, marital status, ethnicity, religion, educational level and occupation status was obtained directly from the patient. Performance status was assessed by applying the Eastern Cooperative Oncology Group (ECOG) scale with 0 'Fully active' to 4 'Completely disabled' [35].

Table 1 Data collection and questionnaires for outcome collection

	Measure	Description
Symptom status and palliative care concerns	Myeloma Patient Outcome Scale (MyPOS) [31]	33-item questionnaire with 15 disease- and treatment-specific symptoms, 13 myeloma-specific quality of life items, 5 generic items about palliative care concerns
		Module of the Palliative Care Outcome Scale [32]
		Three subscales: Functioning and symptoms, Emotional response, Healthcare support (information and satisfaction with care) [31]
		5-point Likert scale (0 – not at all to 4 – overwhelming)
		Possible range of 0–132 for total score (higher score means more symptoms/problems)
Health-related quality of life	European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 [26]	30-item generic health-related quality of life questionnaire
		Five functional scales (physical, role, emotional, social, cognitive functioning), six symptom scales (fatigue, nausea/vomiting, pain, dyspnoea, constipation, appetite loss, sleeping problems, financial difficulties), one global health status/quality of life scale
		4-point Likert scale (1 – not at all to 4 – very much), except for two 7-point global health status/quality of life items
		Transformation of all scales to 0–100 scale [30]
		High scores on functional scales and global quality of life scales represent high level of functioning/quality of life
		High scores on symptom scales represent a high symptom burden
	EORTC-QLQ-MY20 [28, 29]	20-item add-on module of disease-specific symptoms and functional impact for multiple myeloma, added onto the EORTC-QLQ-C30
		Two symptom subscales (disease symptoms and side-effects of treatment), two functional subscales (body image and future perspectives)
		4-point Likert scale (1 – not at all to 4 – very much)
		Transformation of all scales to 0–100 scale
		High scores on functional scales represent high levels of functioning. High scores on symptom scales represent a high symptom burden.
	EuroQOL-5D-3L [27]	Time trade-off utility measure from a 5-item health status assessment and a visual analogue scale (generic health state outcome)
		5 items: mobility, self-care, usual activities, pain/discomfort, anxiety/depression; global health status measured by one visual-analogue scale (0–100)
		3-point Likert scale for 5 items (no problems, some/moderate problems, extreme problems)
		Five items form EQ5D Index score, transformed into health status
		Range of −0.59 to 1.0 points (higher scores indicate better health state with 1.0 representing full health), standardised according to country-specific norms (UK and US norms)

Disease and treatment details extracted from medical records

Disease and clinical details were extracted from the patient's medical notes. These were information on the date of diagnosis, the immunoglobulin type (Ig), and the clinical stage of myeloma. The International Staging System (ISS) [36] for myeloma was used to stage the disease at diagnosis on the basis of the reported β_2-microglobulin and albumin parameters in the clinical notes. Time since diagnosis in months as a measure of disease duration was calculated by subtracting the date of the interview from the data of diagnosis. The current phase of illness was classified as newly diagnosed (pre-treatment or undergoing first-line treatment), being in a treatment-free interval (watch and wait or stable disease with no evidence of disease progression) or relapsed/progressive disease (second line therapy or above, lack of response or progression on treatment or receiving palliative care) [37].

Treatment details were also extracted from the medical records. It was recorded whether patients were currently on treatment, the types and dates of current and previous treatments and the response to these treatments [38]. From this information, a classification was derived of current and previous treatments, treatment intensity, number of lines of treatment received and whether patients were in a treatment or a treatment-free interval at the time of the survey. A treatment line was defined as any active or maintenance treatment a patient received for their myeloma disease, either as first-line treatment or after a relapse. Treatment-free intervals were intervals during which patients were classified as being in remission, receiving no active or maintenance treatment or receiving supportive treatments only (e.g. anaemia medication or bisphosphonates).

Statistical analysis

Apart from one item (worry about sex life) on the MyPOS, missing data were less than 5 % of participants on most dependent and independent variables and tested to be missing at random. For descriptive analyses we did not impute missing values [39]. Handling of missing data in the multivariate analyses involved running a complete-case analysis as the first step und using multiple imputation in a second step [40].

Data analysis for objective (a), the description of symptom severity, palliative care concerns and HRQOL, involved determining the point prevalence with 95 % confidence intervals of MyPOS symptoms (if reported at least as 'slight'). The X^2-test was used for comparison of symptom burden across disease phases. The total MyPOS score (total palliative care concerns) and subscale scores of the MyPOS were compared between disease phases using univariate analysis of variance.

For objective (b), determining the factors associated with a lower quality of life and higher palliative care concerns, we used multiple linear regression models. The total MyPOS score, global quality of life scale of the QLQ-C30 and the EQ5D Index were the dependent variables and symptom and patient characteristics were independent variables. We built regression models for each outcome variable separately. Data cleaning and testing of assumptions for regression techniques (normality, skewness, kurtosis, outliers, linearity) were performed before analysis [39]. Total scores on the MyPOS, the EORTC and EQ 5D questionnaires satisfied assumptions for multivariate analysis. Multicollinearity assessment showed multicollinearity of the physical functioning subscale in the EORTC-QLQ-C30 and the "mobility" item in the MyPOS. The latter, due to its better statistical distribution, was kept in the analysis. The following strategy was used to prioritise variables for inclusion in the models: univariate linear regression models tested each of the 15 symptoms against the three outcomes. Those that were statistically significant (Bonferroni-corrected alpha level <0.003) were combined in a multivariate model that was then trimmed to exclude variables that lost significance. The initial set of clinical, treatment and demographic variables was based on a systematic review of predictors for HRQOL in multiple myeloma [41].

To test objective (c), determining whether general symptom level had a stronger influence on HRQOL than disease characteristics, we used hierarchical regression procedures. We adjusted models for each outcome variable for the influence of general symptom level (total number of symptoms on the MyPOS). Socio-demographic, disease and treatment history variables as well as HADS depression and anxiety scores found to be significant in bivariate analyses were entered into the multivariate model, which was further reduced by excluding non-significant factors.

Sample size calculations in G*Power software [42] for multiple linear regression analyses using 15 predictors, power = 80 %, $\alpha = 0.05$ and a medium effect size of $F = 0.15$ for regression [43] suggested a sample size of 139, which was well exceeded in this analysis.

All analyses were conducted using SPSS 22 [44].

Ethical issues

Research Ethics Committee approval was granted by the South East London REC-3 (ref 10/H0808/133) and by the Central London REC (13/LO/1140). Local permissions from the Research & Development departments of all 18 participating NHS hospital trusts were obtained. A complete list of participating trusts can be found in the Declarations section.

Results

Overall, 1041 patients with multiple myeloma were screened in both studies, of which 869 fulfilled the inclusion criteria and were approached. Completed questionnaires were received from 557 participants. One-hundred-seventy-two patients were ineligible for recruitment, 218 declined to participate and 33 were consented but the completed questionnaire was not received. Reasons for ineligibility and non-participation are detailed in Fig. 1.

Table 2 displays the sample characteristics of 557 myeloma patients. Their mean age was 68.4 years (SD 10.4; median: 69 years, range: 34–92 years) with a higher proportion of men taking part (61.4 %). Most participants were in a treatment-free interval; a mean 42.5 months post diagnosis; 139 (25.5 %) patients had been living with myeloma 5 years or longer. Two-hundred-fifty-eight (46.5 %) participants were currently not on active or maintenance treatment. The median number of lines of treatment received was one.

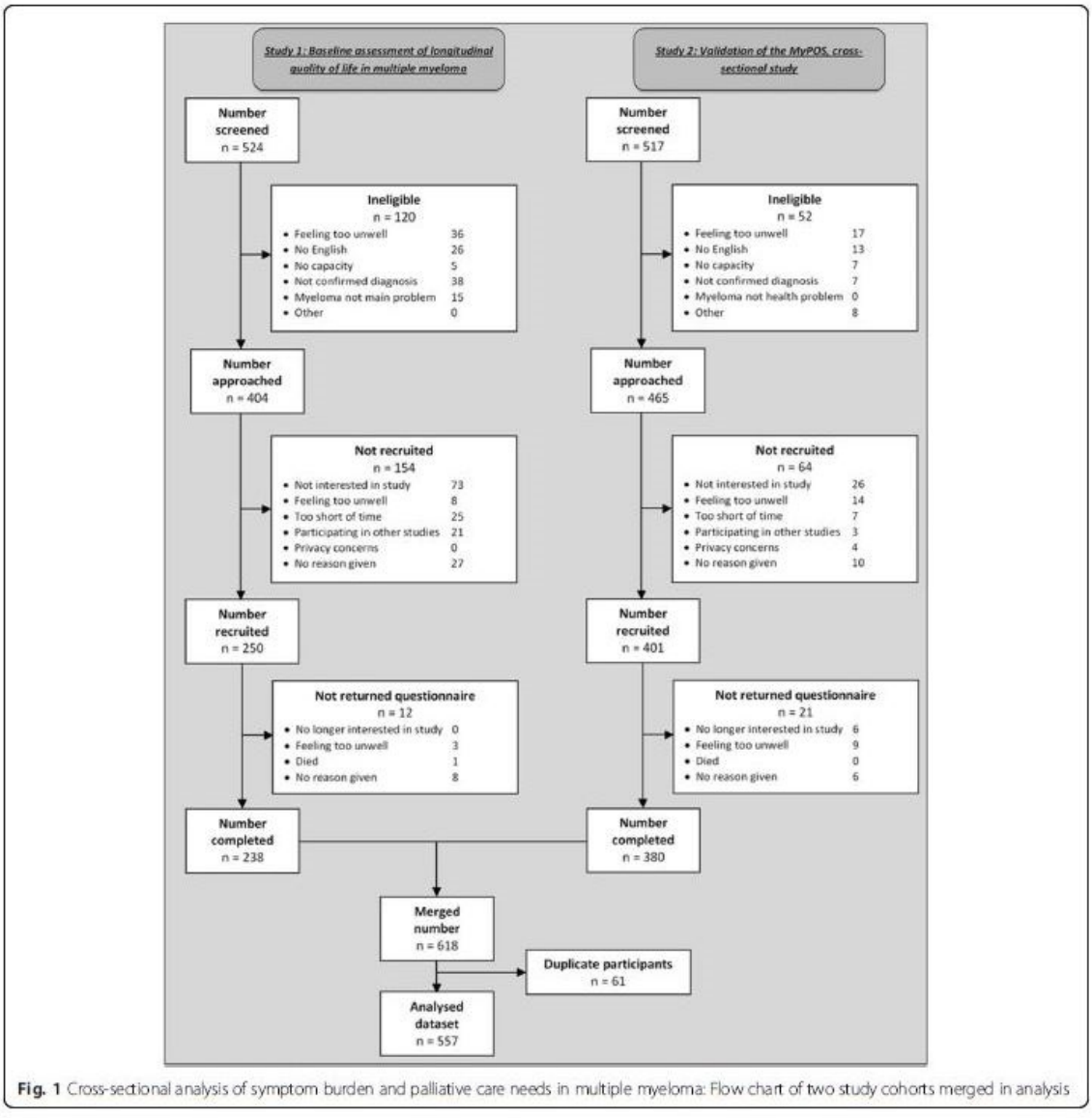


Fig. 1 Cross-sectional analysis of symptom burden and palliative care needs in multiple myeloma: Flow chart of two study cohorts merged in analysis

Table 2 Demographic and clinical characteristics of 557 patients with myeloma included in the study

Variable	Patients *n*	%
a) Socio-demographic details		
Age: Mean (SD, range)	68.41	(SD 10.4; 34–92)
Gender		
Men	341	61.2
Women	209	37.5
Missing	7	1.3
Ethnicity		
White British/Irish/Other white background	513	92.1
Black African or Black Caribbean	19	3.4
Mixed ethnic background	4	0.7
Other	14	2.5
Missing	7	1.3
Marital status		
Single	44	7.9
Married	400	71.8
Divorced or separated	36	6.5
Widowed	68	12.2
Missing	9	1.6
Occupational status		
Working or student	82	14.7
Not working or retired	467	83.9
Missing	8	1.4
b) Disease factors		
Current phase of illness		
Newly diagnosed	102	18.3
Treatment-free interval/stable disease	266	47.8
Relapsed/progressive/palliative stage	182	32.7
ISS stage at diagnosis		
I	154	27.6
II	109	19.6
III	116	20.8
Missing	178	32.0
Time since diagnosis in years: Mean (SD)	3.53	(3.4)
Median, range (in years)	2.5	(0.08–23.6)
Immunoglobulin type		
IgG	314	56.4
IgA	118	21.2
Kappa or lambda light chain	95	17.1
Other	15	2.7
Missing	15	2.7
ECOG performance status		
0 Fully active	188	33.8
1 Restricted	222	39.9
2 Unable to work	87	15.6
3 or 4 – Limited selfcare/confined	50	9.0
Missing	10	1.8
Total number of symptoms on MyPOS		
0	5	0.9
1–5	175	31.4
6–8	168	30.2
9–15	205	36.8
Missing	4	0.7
d) Treatment factors		
Lines of treatment: Median (range)	1	(0–6)
Previously untreated	30	5.4
1 line received	249	44.7
2 lines received	155	27.8
3 or more lines received	123	22.1
Currently on treatment	292	52
Active chemotherapy	213	–
Undergoing autologous stem cell transplant	5	–
Maintenance therapy	74	–
Current MM treatment		
Bortezomib	59	27.6
Lenalidomide	89	41.9
Thalidomide/Pomalidomide	56	26.5
Alkalyting agent	111	51.9
Other	2	0.9
Combination chemotherapy	110	51.4
Intensity of treatments received		
None	54	9.7
Chemotherapy only	303	54.4
Chemotherapy and stem cell transplant	161	28.9
More than one transplant	32	5.7
Missing	7	1.3

Abbreviations: *ECOG* Eastern Cooperative Oncology Group performance status, *ISS* International staging system classification of myeloma [36], *MyPOS*: Myeloma Patient Outcome Scale, *SD* Standard deviation

Prevalence of myeloma-specific symptoms and concerns

Patients reported a mean of 7.2 symptoms (SD = 3.3, median: 7, range: 0–15). The most burdensome symptoms, scored as 'severe' or 'overwhelming' on the MyPOS, were fatigue (with 21.9 % scoring it as burdensome), pain (13.8 %), and tingling in the hand/feet

(10.2 %) (Fig. 2 and Additional file 1: Table S1). Three symptoms were present in 60–88 % of patients - pain (71.5, 95 % CI: 67–76 %), fatigue (87.6, 95 % CI: 85–90 %) and breathlessness (60.8, 95 % CI: 57–65 %). Difficulty remembering things, tingling in the hand/feet and poor mobility were present in 50–70 % of participants. Less prevalent symptoms were constipation (38.3 %), mouth problems (sore or dry mouth, 37.3 %), anxiety (31.5 %), nausea (29.3 %), diarrhoea (23.2 %), depression (22.8 %) and vomiting (10.1 %).

The most burdensome problems and concerns existed in the domains functioning, emotional wellbeing, and information needs. These included problems with carrying out usual activities (32.3 %); worrying that the illness might get worse (40.4 %), and not having enough information about what might happen in the future (29.4 %). The mean total MyPOS score was 21.5 (SD = 13.4), indicating a moderate level of concerns.

Symptoms and concerns per treatment phase

The prevalence and severity of symptoms differed according to disease phase. Of the three groups – newly diagnosed, treatment-free interval, and relapsed/progressive disease - those with relapsed/progressive disease had the highest mean number of symptoms ($M = 5.91$, SD = 2.63; versus $M = 4.91$ in the newly diagnosed group and $M = 4.77$ in a treatment-free interval). On the symptom level, differences between disease phases were found for shortness of breath (X^2: 12.5, $p = 0.002$), constipation (X^2: 8.1, $p = 0.018$), mouth problems (X^2: 9.98, $p = 0.007$), and tingling in the hands and feet (X^2: 18.93, $p < 0.001$) with more patients in the relapsed/progressive phases of disease suffering from these symptoms than expected (Table 3).

Similarly, patients with relapsed/progressive disease had the highest mean total MyPOS score ($M = 24.68$), followed by newly diagnosed patients ($M = 23.1$) and patients in a treatment-free interval ($M = 18.8$). On the subscale level, univariate analysis of variance showed that differences exist in Functioning/Symptoms ($F = 11.919$, $p = 0.001$) and the Emotional response subscale ($F = 5.36$, $p = 0.005$) between the phases with post-hoc tests indicating that patients with relapsed and progressive disease have more problems in these areas than those in the stable phases of myeloma (Fig. 3).

A more fine-grained analysis of phase according to treatment (number of treatment lines or treatment-free interval), shown in Fig. 4, was conducted to better

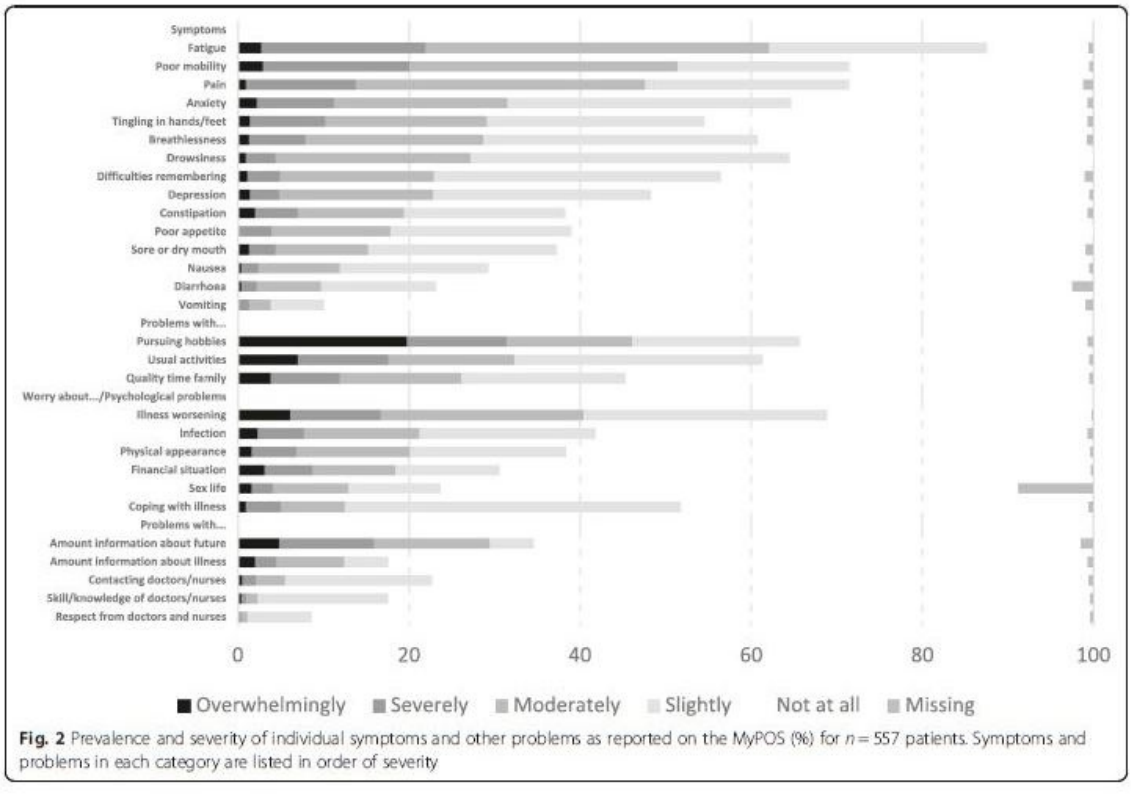


Fig. 2 Prevalence and severity of individual symptoms and other problems as reported on the MyPOS (%) for $n = 557$ patients. Symptoms and problems in each category are listed in order of severity

Table 3 Outcome data scores for total sample and comparison of symptoms and palliative care needs across disease phases

	Score			Newly diagnosed ($n = 102$)			Stable ($n = 268$)			Progressive, relapsed stage ($n = 184$)			Test	
Measure	*n*	Mean, SD	Median (range)	*n*	Mean, SD	Median (range)	*n*	Mean, SD	Median (range)	*n*	Mean, SD	Median (range)	*F* value	*p*
Time since diagnosis (months)	552	42.3 (40.7)	29.9 (0.1–283)	102	10.4 (16.8)	4.6 (0.2–103.1)	267	44.2 (39.8)	30.4 (0.49–239.9)	183	57.3 (41.8)	57.3 (41.8)	52.2	**0.001***
ECOG Performance status	551	–	1 (0–4)	101	–	1 (0–3)	268	–	1 (0–4)	182	–	1 (0–4)	X^2: 24.4	**0.002**
MyPOS[a]														
Total score	468	21.5 (13.5)	19 (0–61)	86	22.9 (13.4)	20 (1–61)	229	18.9 (13.1)	17 (1–59)	150	24.7 (13.4)	23 (0–61)	96	**0.001**
Symptoms and function	526	76.2 (16.6)	78.8 (30.4–100)	96	75.8 (14.5)	76.8 (36–100)	253	79.1 (14.3)	80.4 (30.4–100)	175	72.2 (14.8)	71.4 (34–100)	11.9	**0.001**
Emotion and coping	499	80 (16.6)	84.4 (18.8–100)	94	77.1 (17.2)	81.3 (34–100)	244	82.4 (16.2)	87.5 (18.8–100)	158	77.9 (16.4)	81.3 (34–100)	5.3	**0.005**
Healthcare support and information needs	544	90.8 (12.7)	95 (40–100)	99	91.2 (12.8)	95 (40–100)	264	91.1 (12.9)	100 (40–100)	178	89.8 (12.5)	95 (50–100)	0.6	0.532
EORTC-QLQ-C30[b]														
Global health status	555	61.2 (22.3)	66.7 (0–100)	102	59.5 (20.5)	66.7 (0–100)	267	65.8 (21.8)	66.7 (0–100)	183	55.2 (22.7)	50 (0–100)	12.9	**0.001**
Physical function	554	61.5 (22.5)	60 (0–100)	101	61.2 (26.7)	66.7 (0–100)	266	65.3 (25.2)	66.7 (0–100)	184	56.2 (24.6)	53.3 (0–100)	6.9	**0.001**
Role function	553	59 (33.1)	66.7 (0–100)	101	55.4 (35.6)	66.7 (0–100)	266	64.9 (30.9)	66.7 (0–100)	183	52.3 (33.5)	50 (0–100)	8.9	**0.001**
Emotional function	555	76.2 (22.1)	83.3 (0–100)	102	74.5 (23.7)	83.3 (0–100)	267	77.3 (21.3)	83.3 (0–100)	183	75.3 (22.3)	75 (0–100)	0.8	0.459
Cognitive function	555	79 (21.9)	83.3 (0–100)	102	78.1 (21.9)	83.3 (0–100)	267	81.2 (20.5)	83.3 (16.7–100)	183	76.3 (23.7)	83.3 (0–100)	2.8	0.060
Social function	554	65.1 (31.5)	66.7 (0–100)	102	60.5 (34.8)	66.7 (0–100)	267	70.2 (29.3)	66.7 (0–100)	182	60.1 (31.7)	66.7 (0–100)	7.1	**0.001**
EORTC QLQ-MY20[c]														
Disease symptoms	549	73.9 (21.2)	77.8 (0–100)	101	75.7 (20.9)	77.8 (0–100)	262	74 (20.9)	77.8 (5.6–100)	183	72.7 (21.8)	77.8 (0–100)	0.6	0.530
Side-effects of treatment	542	81.4 (14.4)	83.3 (0–100)	100	80.3 (14)	83.3 (43–100)	261	83.5 (14)	86.7 (30–100)	178	78.8 (14.9)	80 (23–100)	6.1	**0.002**
Body image	551	77.9 (30.5)	100 (0–100)	100	79 (31.7)	100 (0–100)	265	79.6 (28.2)	100 (0–100)	183	74.9 (32.8)	100 (0–100)	1.4	0.247
Future perspective	549	64.6 (26.5)	66.7 (0–100)	100	61.4 (28.1)	66.7 (0–100)	264	67.2 (25.1)	77.8 (0–100)	182	62.1 (27.3)	66.7 (0–100)	2.8	0.061
EuroQOL-5D-3L														
EQ5D Index score	550	0.65 (0.28)	0.69 (−0.5–1)	101	0.66 (0.28)	0.69 (−0.18–1)	264	0.67 (0.27)	0.69 (−0.18–1)	182	0.59 (0.29)	0.69 (−0.35–1)	4.5	**0.012**
EQ5D Visual analogue scale VAS	318	63.51 (20.02)	61 (0.5–100)	68	58.8 (19.8)	60 (0.5–96)	139	69 (19.6)	69.5 (11–100)	111	59.5 (19.1)	60 (10–100)	9.82	**0.001**

[a]MyPOS: Myeloma Patient Outcome Scale: comprises 27 items, higher scores indicate higher symptom burden/more palliative care needs, MyPOS subscale scores transformed to 0–100 scale to allow for comparison to subscale scores from the EORTC QLQ-C30 and –MY20 questionnaires

[b]EORTC QLQ-C30: For the EORTC-QLQ-C30, higher scores on functioning subscales and the global quality of life scale indicate better functioning/better quality of life

[c]EORTC-QLQ-MY20: For the myeloma module of the EORTC quality of life questionnaire higher scores indicate more problems/symptoms in subscales

*Bold values denote significant p-values (>0.05)

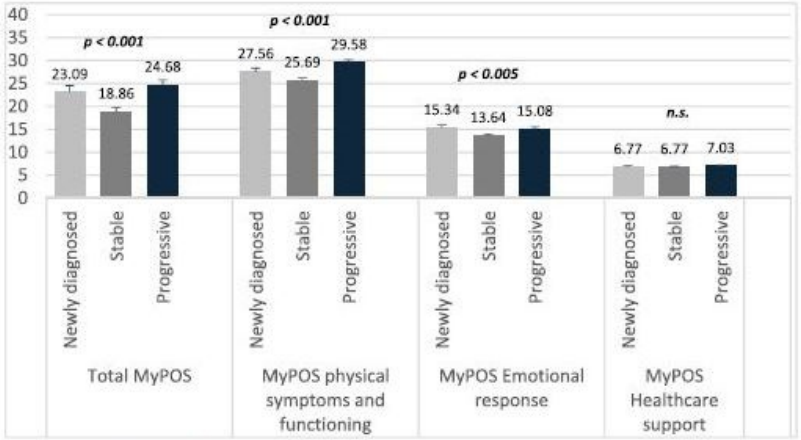
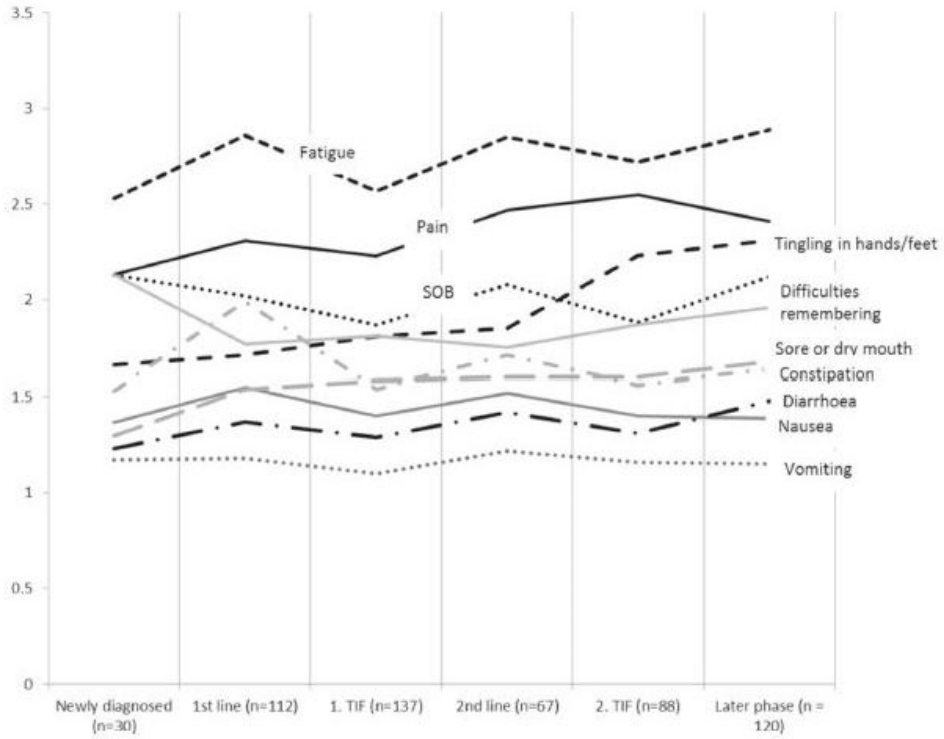


Fig. 3 Differences in the total MyPOS and MyPOS subscales in three phases of myeloma disease



Line: line of treatment, MyPOS: Myeloma Patient Outcome scale, SOB: Shortness of breath, TIF: treatment-free interval

Fig. 4 Mean MyPOS symptoms and subscale scores per treatment phase. A higher score indicates a higher symptom burden in the individual symptom items. *Line* line of treatment, *MyPOS* Myeloma Patient Outcome scale, *SOB* Shortness of breath, *TIF* treatment-free interval

understand the differences in symptom burden and problems according to phase. The symptoms fatigue, pain and shortness of breath showed a high severity throughout all treatment phases, with the latter being overtaken by tingling in the hands and feet as the third most severe symptom from the second treatment-free interval onwards. Scores for all symptoms tended to be higher during treatment-intervals than in treatment-free intervals. Scores for sore or dry mouth, diarrhoea, tingling in the hands/feet, shortness of breath and difficulties remembering were highest for those participants in the later phases of disease.

Factors associated with myeloma-specific problems and concerns

All symptoms and functioning scales of the EORTC QLQ-C30 were significantly associated in bivariate analyses with the total MyPOS score. The only demographic characteristic being associated with high palliative care concerns was age (see Additional file 1: Tables S2 and S3). Clinical characteristics that were significantly different for those in the lower vs higher half of the MyPOS total score distribution were phase of illness (with a higher proportion of newly diagnosed and relapsed patients reporting a higher MyPOS total score), receiving treatment, an ECOG performance status of 2 and general symptom level. In the first multivariate model and after adjusting for general symptom level, only the symptoms fatigue, pain, anxiety, dry mouth and the physical function and social function subscales remained significantly independently associated with the outcome. The final parsimonious multivariable model with demographic and clinical factors showed significant associations of general symptom level, pain, anxiety, dry mouth, physical function, age, and being either in the newly diagnosed or relapsed/progressive disease phase with high palliative care concerns (see Table 4).

Multiple regression analysis of quality of life

In the first multivariate model including all symptoms and demographic and clinical characteristics found positively associated in the bivariate analyses (see Additional file 1: Tables S2 and S3), only the symptoms pain, fatigue, anxiety and depression as well as poor mobility

Table 4 Regression models for outcome variables a) palliative care concerns (total MyPOS score), b) global quality of life (EORTCQLQ-C30 subscale), and c) generic health-related quality of life (EQ5D Index score) and their association with demographic, clinical characteristics and symptom burden ($n = 557$)

	Palliative care concerns			Global quality of life QLQ-C30			EQ5D Index		
Independent variables	Coefficient	Lower CI	Upper CI	Coefficient	Lower CI	Upper CI	Coefficient	Lower CI	Upper CI
(Constant)	20.639**	14.189	27.089	105.788**	100.986	110.589	1.168**	1.093	1.242
General symptom level	1.439**	1.136	1.741	–	–	–	–	–	–
Pain	0.046*	0.016	0.076	−2.572*	−4.168	−0.975	−0.100**	−0.129	−0.071
Weakness/lack of energy	–	–	–	−5.741**	−7.395	−4.086	–	–	–
Drowsiness	–	–	–	–	–	–	0.032	0.000	0.064
Dry mouth	1.395**	0.558	2.233	–	–	–	–	–	–
HADS Anxiety	1.100**	0.891	1.308	−2.519*	−4.091	−0.947	–	–	–
HADS Depression	–	–	–	−3.749**	−5.446	−2.052	−0.075**	−0.102	−0.048
Age	−0.136**	−0.204	−0.069	–	–	–	–	–	–
Being in the stable/plateau phase[a]	−2.693**	−4.096	−1.290	4.804**	2.127	7.482	–	–	–
ECOG performance status 2[b]	–	–	–	−3.654	−7.449	0.141	–	–	–
ECOG performance status 3/4 – limited self-care or completely disabled[c]	–	–	–	–	–	–	−0.159**	−0.248	−0.070
Physical function/Poor mobility	−0.138**	−0.174	−0.101	−5.085**	−6.610	−3.560	−0.082**	−0.110	−0.054
Adjusted R^2	0.879			0.514			0.584		
F, P	$F = 192.205$	$P < 0.001$		$F = 85.522$	$P < 0.001$		$F = 61.924$	$P < 0.001$	

ECOG Eastern Cooperative Oncology Group performance status, *CI* confidence interval, *EQ5D* EuroQol-5D-3L, *HADS* Hospital Anxiety and Depression Scale, *MyPOS* Myeloma Patient Outcome Scale

[a]Reference group is patients being unstable, i.e. newly diagnosed or having relapsed, progressive or palliative disease or being in a treatment-interval

[b]Reference group is ECOG performance status of 0

[c]Reference group is ECOG performance status of 0

*$p < 0.05$

**$p < 0.001$

remained significant in their association to the global quality of life item of the QLQ-C30. Controlling for general symptom level did not alter the results. In the final multivariate trimmed model, the quality of life score was significantly and independently associated with a higher pain level, higher fatigue level, more mobility problems, more anxiety and depression and an ECOG performance status of 2 (Table 4). Those in a treatment-free interval experienced better quality of life. The final multivariate trimmed model for the outcome EQ5D Index score contained the variables pain, drowsiness, poor mobility, depression and ECOG performance status of 2, but no effect of phase of illness was found, nor an effect of general symptom level (Table 4).

Discussion

This is the first study to compare levels of symptom burden and quality of life problems among patients at different stages of the disease. We found a persistently high symptom burden, even during treatment-free phases of disease in multiple myeloma, and providing evidence for the association and potential mediation of general symptom level, pain, fatigue, mental health and physical function on disease-related problems and HRQOL.

The findings demonstrate the persistently high symptom burden and compromise in HRQOL, expressed by a high mean number of symptoms, with pain, fatigue, symptoms of peripheral neuropathy and breathlessness as the most commonly reported symptoms. These persist into the later stages of myeloma, thereby confirming results from the Nordic Myeloma Study group [10] and from the Eindhoven Profiles registry [11] regarding the high symptom burden and the importance of pain, fatigue and breathlessness, together with symptoms of peripheral neuropathy, in myeloma. Our analysis expands these findings by showing that symptoms may well extend and remain a burden in the treatment-free intervals. A similar persistent high prevalence of pain, neuropathic and other, and fatigue was observed by Boland and co-authors in a sample of patients with multiply relapsed but stable disease [23]. A lower HRQOL in global and subdomains of the EORTC QLQ-C-30 and MY-20 measures was also described in a cross-sectional study by Acaster et al. [6], suggesting persistent symptom burden. However, it should be borne in mind that these findings come from cross-sectional studies. Longitudinal observational evidence in myeloma is rare, with the few studies not using secondary analysis of RCT data enrolling patients at the stage directly pre or post first-line treatment and not focusing on advanced stages [17–22].

One surprising finding was the high prevalence of breathlessness that was reported by 60.8 % of participants. The severity of shortness of breath had a mean of close or above 2.0 in all treatment phases – from diagnosis and prior to first-line treatment to later phases post the second treatment-free interval. However, this finding might be explained by cardiac or pulmonary complications either resulting from the disease itself, from treatments received (with patients receiving immunomodulatory agents or bortezomib being at increased risk of experiencing pulmonary adverse events) [45, 46], or – given that our study included a predominantly older population with a mean age of 68.4 years – also being a consequence of age-related comorbidities [47]. A limitation of our study is that number of comorbidities was not assessed and that lack of assessing this potential confounder might affect the relationship between symptoms, performance status and palliative care concerns or quality of life. Future studies should focus on the relationship between comorbidity, treatment intensity, disease progression and HRQOL [48].

To better understand which patients with multiple myeloma would profit from targeted supportive care interventions, a regression analysis of associations between patient, disease, treatment characteristics and palliative care concerns or quality of life was conducted. Multiple myeloma, despite being an incurable disease with patients ultimately dying from it, its related complications, or from the side effects of treatment, is still not recognised as a disease that warrants palliative care involvement [49]. This is mainly due to the disease, like many other haematological cancers, not following a linear trajectory of progression in which the end of life is well-defined. Rather, the progression is interspersed with intermittent periods of remission and stable disease, relapse, multiple lines of treatment, the potential for sudden deterioration and death due to disease- or treatment-related complications and patients continuing to receive and to respond to treatment even in advanced disease [50–52]. Our finding of a persistently high symptom burden, even during treatment-free intervals, shows that decisions regarding involvement of palliative care to support and help with the impact on quality of life cannot be based on clinical response to treatment as this will miss a substantial number of patients who would benefit from additional supportive or palliative care services [53, 54]. This matters because research on needs in general cancer and myeloma has shown that those patients with high unmet needs, low quality of life and a high symptom burden are at increased risk of shortened survival [55–57].

Results from regression analyses support other authors' findings of patient's self-reporting of symptoms providing independent prognostic information [8, 55, 57]. However, contrary to our hypothesis, we found that general symptom level did not act as a mediator in the

hierarchical regression analyses for all outcomes. This means it is not the high number of symptoms that might indicate who is in need of supportive care, but specific symptoms might better serve that purpose. Especially the presence of pain or fatigue indicates burden and is associated with high palliative care concerns; results that are similar to findings by Kripp et al. [54]. In our study, general symptom level did not remain independently associated with global quality of life when sociodemographic and clinical variables were entered into the regression analysis, contrary to a recent study using a different outcome measure to determine general symptom level [12]. This might be because Jordan et al. [12] did not take into account variables like functioning. Our findings from the regression analyses support the hypothesised relationships between symptoms, function, emotional response and quality of life in the Wilson and Cleary model [58].

Contrary to the study of predictors for survival in myeloma [38], clinical variables such as ISS stage, myeloma subtype or treatment-related variables did not remain significantly independently associated with quality of life in our study. Other factors, such as low performance status and pain, do overlap. Depression and anxiety were significant factors for all three outcomes. The importance and persistence of mental health problems have been demonstrated in other studies, also as predictors for survival [55, 57]. Overall, this points towards patients needing more support in all phases and that focusing resources on the end of life, which is hard to define in multiple myeloma, or clinical response criteria misses a potentially large number of patients who experience a high burden of disease- and treatment-related problems. Early integration of palliative care, alongside monitoring of HRQOL and symptoms, could help targeting supportive care services towards those in need and might help better symptom management. These approaches have shown to be valuable in monitoring treatment adverse events in haematology [59, 60].

Our study had several limitations. Despite the high response rate, this was a cross-sectional study with non-random sampling. Selection bias might limit the validity of the findings. Although many of the screened and eligible patients for the study took part and we aimed to recruit a consecutive sample, there was some non-response. Among the reasons for declining to take part "feeling too unwell" or considering the study "too burdensome" were most frequently named, suggesting that those who declined might have had more symptoms and concerns and also might have had more difficulties coping with the consequences of myeloma and its treatment. However, this did not hinder us to recruit a substantial number of patients with relapsed or progressive disease (32.7 %). The high number of patients during treatment-free intervals and with stable disease points towards the fact that the results from this study under-represent the views of those that might have a shorter and more acute disease trajectory and more severe symptoms. Prevalence estimates for symptoms might therefore be biased towards under-estimation.

The majority of patients were recruited from tertiary cancer centres, although we tried to obtain a mix of recruiting centres. More patients were sampled from out-patient than from in-patient clinics. This led to an under-representation of patients receiving stem cell transplant at the time of the study (5 %) and might have imbalanced the sample towards those with higher functional performance status (only 9 % of patients had an ECOG performance status of 3 or 4). A diverse patient group was included with diverse treatment histories which makes it difficult to distinguish between disease symptoms and treatment-related toxicities. A further limitation of our study is the lack of collecting information on co-morbidities for patients. This information was only available for a part of the sample and could not be obtained validly from all medical notes. We are aware that it is therefore not possible to understand this potential confounding factor.

This study uses a cross-sectional design. Therefore, independent variables in the regression analyses and any correlation reported represent association but no prediction. Moreover, this study did not follow patients as they naturally progressed through different phases of disease. Comparison between phases therefore relies on comparison between different patients. Physiological variables like haemoglobin, albumin or other variables that indicate disease activity were not extracted from the medical records and could not be considered in the regression analysis.

Conclusions

This study showed the importance of regular assessment of symptom burden and of quality of life in routine clinical care. The current practice of one single holistic needs assessment potentially misses periods of persistently high problems, specifically pain, fatigue, breathlessness but also mental health problems that occur during the advanced stages and even during treatment-free intervals. The early integration of supportive and palliative services for those experiencing high physical and emotional symptoms could help improve symptom management and therefore help maintain or optimise patient's quality of life. Focusing on traditional parameters to monitor the disease progression might not help identify those patients with myeloma that experience a low quality of life.

Additional file

Additional file 1: Figure S1. Myeloma Patient Outcome Scale (MyPOS). All questions are preceded by "Over the past week…". **Table S1.** Prevalence and severity of myeloma-specific symptoms and problems (MyPOS) in 557 multiple myeloma patients. **Table S2.** Univariate associations of symptoms with EORTC QLQ –global quality of life scale, EQ5D index and visual analogue (VAS) scale scores and the Myeloma Patient Outcome Scale total score, using linear regression with bootstrapping (1000 samples). **Table S3.** Bivariate associations of independent variables with the the outcomes a) MyPOS total palliative care concerns, b) EQ5D Index, d) Global health status (EORTC QLQ-C30), $n = 557$. (DOCX 42 kb)

Abbreviations

CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire C30; EORTC QLQ-MY20, European Organization for Research and Treatment of Cancer (EORTC) myeloma-specific quality of life questionnaire MY20; EQ5D, EuroQOL group health status questionnaire 5D-3L; HADS, Hospital Anxiety and Depression Scale; HRQOL, health-related quality of life; Ig, immunoglobulin type; ISS, International Staging System; M, mean; MyPOS, Myeloma Patient Outcome Scale; n.s., non-significant; SD, standard deviation; SOB, shortness of breath; TIF, treatment-free interval; UK, United Kingdom; US, United States of America.

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Availability of data and materials

The authors have full control over the primary data. As per the research ethics committee approval, this dataset is subject to the UK data protection regulations and can only be reviewed in anonymised form by researchers directly supervised by Professor Irene J. Higginson at the Cicely Saunders Institute, Department of Palliative Care, Policy and Rehabilitation, Faculty of Life Sciences and Medicine, King's College London, Bessemer Road, Denmark Hill, London SE5 9PJ, United Kingdom, email: irene.higginson@kcl.ac.uk.

Authors' contributions

IJH led the application for funding in collaboration with SAS, RJS and PME, who designed the overall study. CR, TR, RJS, WG, PME, SAS and IJH contributed to the conception, design and conduct of the study with IJH acting as senior researcher overseeing the project. CR drafted the manuscript. All other authors provided comments and critical revisions. The final manuscript was approved by all authors prior to submission. CR and IJH are co-guarantors.

Competing interests

The authors declare that they have no competing interests.

Consent for publication

Not applicable.

Ethical approval and consent to participate

Research Ethics Committee (REC) approval in the United Kingdom where this study took place was granted by the South East London REC-3 (reference number 10/H0808/133) and by the Central London REC (reference number 13/LO/1140). Local permissions from the Research & Development departments of all 18 participating NHS hospital trusts were obtained. The Research & Development departments of the following trusts gave their permission: Bradford Teaching Hospitals NHS Foundation Trust, Burton Hospitals NHS Foundation Trust, Colchester Hospital University NHS Foundation Trust, East Cheshire NHS Trust, Epsom and St Helier University Hospitals NHS Trust, Frimley Park Hospital NHS Foundation Trust, Guy's and St Thomas' NHS Foundation Trust, King's College Hospital NHS Foundation Trust, Maidstone and Tunbridge Wells NHS Trust, Medway NHS Foundation Trust, Mid Yorkshire Hospitals NHS Trust, Northampton General Hospital NHS Trust, Pennine Acute Hospitals NHS Trust, Royal Free London NHS Foundation Trust, Surrey and Sussex Healthcare NHS Trust, University Hospital Coventry and Warwickshire NHS Trust, Weston Area Health NHS Trust, and Wye Valley NHS Trust. Written informed consent was obtained from each of the participants in the study.

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SUPPLEMENTAL MATERIALS

Figure S1. Myeloma Patient Outcome Scale (MyPOS). All questions are preceded by "Over the past week…".

1	What are your main problems or concerns at the moment?	[Open question with three empty boxes for respondent to complete, numbered 1-3]				
2	Below is a list of symptoms, which you may or may not have experienced. For each symptom please tick one box that best describes how it has affected you over the past week:	Not at all	Slightly	Moderately	Severely	Over-whelmingly
a	Pain	I have not had this symptom in the past week	Little or no effect on activities or concen-tration	Some effect on activities or concen-tration	Marked effect on activities or concen-tration	Unable to think of anything else
b	Fatigue or lack of energy					
c	Shortness of breath					
d	Diarrhoea					
e	Constipation					
f	Nausea (feeling like you are going to be sick)					
g	Vomiting (being sick)					
h	Mouth problems					
i	Poor mobility					
j	Tingling in the hands and / or feet					
k	Difficulty remembering things					
l	Please list any other symptoms not mentioned above, and tick one box to show how they have affected you over the past week:	[Three boxes beneath symptoms list for respondent to add additional symptoms, numbered 1-3]				
3	Have you been able to carry out your usual activities without help from others?	Yes, as much as I wanted	Most of the time	Sometimes	Occasionally	No, not at all
4	Have you been able to pursue your hobbies and leisure activities?					
5	Have you been able to spend quality time with family and friends?					
6	Have you been worrying about your sex life?	No, not at all	Occasionally	Sometimes	Most of the time	Yes, always
7	Have you been feeling depressed?					
8	Have you been feeling anxious or worried about your illness or treatment?					
9	Have you been worrying about infections?					
10	Have you been worrying about your physical appearance?					
11	Have you been worrying about your financial situation?					
12	Have you been worrying that your illness will get worse?					
13	Have you felt able to cope with your illness and treatment?	Yes, always	Most of the time	Sometimes	Occasionally	No, not at all
14	Are you able to contact your doctors or nurses for advice if needed?					
15	Do your doctors and nurses show a good standard of knowledge skill when treating you?					
16	Do your doctors and nurses show care and respect when treating you?					
17	Do you have enough information about your illness and treatment?	Enough Information	Information received	Information received	Very little information	No information received
18	Do you have enough information about what might happen to you in the future?	the right amount for me	but hard to understand	but would like more	and would like more	and would like information

Table S1. Prevalence and severity of myeloma-specific symptoms and problems (MyPOS) in 557 multiple myeloma patients

			Prevalence	95% CI	Not at all (0)		Slight (1) or Moderate (2)		Severe (3) or Overwhelming (4)		Missing data
	M	SD	n (%)		n	%	n	%	n	%	%
Symptoms											
Pain	1.35	1.05	398 (71.5%)	67-76%	152	27.3	321	57.7	77	13.8	1.2
Breathlessness	0.99	0.99	339 (60.9%)	57-65%	214	38.4	295	52.9	44	7.9	0.8
Fatigue	1.75	0.99	488 (87.6%)	85-90%	66	11.8	366	65.7	122	21.9	0.6
Nausea	0.44	0.78	163 (29.3%)	25-33%	391	70.2	150	26.9	13	2.4	0.5
Vomiting	0.15	0.51	56 (10.1%)	7-13%	496	89.0	49	8.8	7	1.3	0.9
Poor appetite	0.61	0.88	218 (39%)	35-43%	337	60.5	196	35.1	22	3.9	0.5
Constipation	0.67	1.00	213 (38.3%)	34-42%	340	61.0	174	31.3	39	7.0	0.7
Sore or dry mouth	0.58	0.89	207 (37.3%)	33-41%	344	61.8	183	32.9	24	4.4	1.1
Drowsiness	0.97	0.89	353 (63.4%)	59-67%	198	35.5	330	59.2	23	4.2	1.1
Poor mobility	1.46	1.15	398 (71.5%)	68-75%	156	28.0	287	51.5	111	20.0	0.5
Diarrhoea	1.46	1.15	129 (23.2%)	20-27%	414	74.3	117	21	12	2.2	2.5
Tingling in hands/feet	0.96	1.06	304 (54.6%)	50-59%	249	44.7	247	44.4	57	10.2	0.7
Difficulties remembering	0.86	0.92	314 (56.5%)	52-61%	237	42.5	287	51.6	27	4.9	1.1
Problems with/ Worry about...											
Usual activities	1.2	1.2	342 (61.4%)	57-66%	212	38.1	244	43.8	98	17.6	0.5
Pursuing hobbies	1.64	1.5	366 (65.7%)	62-70%	187	33.6	191	34.3	175	31.4	0.7
Spending quality time with family/friends	0.87	1.16	252 (45.3%)	41-50%	302	54.2	186	33.4	66	11.9	0.5
Sharing feelings with family	0.89	1.2	245 (45%)	41-49%	304	54.5	168	31.1	77	13.9	1.5
Sex life	0.46	0.9	132 (23.7%)	20-28%	376	67.5	109	19.6	23	4.1	8.8
Feeling depressed	0.78	0.96	269 (48.3%)	44-53%	285	51.2	242	43.5	27	4.8	0.5
Feeling at peace	2.38	1.14	439 (78.9%)	76-82%	110	19.8	345	62.1	94	16.8	1.3
Anxious about illness/treatment	1.1	1.05	360 (64.7%)	60-69%	193	34.6	298	53.5	62	11.2	0.7
Family anxious/worried about patient	1.23	1.14	369 (66.1%)	62-70%	179	32.2	284	50.9	85	15.2	1.7
Infection	0.74	1.04	233 (41.8%)	38-46%	320	57.5	190	34.1	43	7.7	0.7
Physical appearance	0.67	1.00	214 (38.4%)	34-43%	341	61.2	176	31.6	38	6.8	0.4
Financial situation	0.61	1.07	170 (30.6%)	28-35%	385	69.1	122	21.9	48	8.7	0.4
Illness worsening	1.32	1.19	384 (68.9%)	65-73%	172	30.9	291	52.2	93	16.7	0.2
Coping with illness/treatment	0.71	0.85	289 (51.8%)	48-56%	265	47.6	261	46.8	28	5.0	0.5
Contacting doctors/nurses	0.31	0.67	127 (22.7%)	19-27%	427	76.7	115	20.6	12	2.1	0.5
Skill/Knowledge of doctors/nurses	0.21	0.53	98 (17.6%)	15-21%	457	82.0	93	16.7	5	0.9	0.4
Respect from doctors and nurses	0.10	0.39	48 (8.6%)	6-11%	507	91.0	46	8.2	2	0.4	0.4
Having enough information about illness/treatment	0.37	0.89	98 (17.6%)	15-21%	455	81.7	73	13.1	25	4.5	0.7
Information about what might happen in the future	0.86	1.29	193 (34.6%)	31-39%	356	63.9	104	18.7	89	15.9	1.4
Addressing practical matters resulting from illness	0.5	0.97	142 (25.5%)	22-29%	405	72.8	106	19.0	36	6.5	1.7
MyPOS Total score	21.5	13.4	range: 0-61								

Table S2. Univariate associations of symptoms with EORTC QLQ –global quality of life scale, EQ5D index and visual analogue (VAS) scale scores and the Myeloma Patient Outcome Scale total score, using linear regression with bootstrapping (1000 samples)

	QL2		EQ5D index		EQ5D VAS		MyPOS total score	
Variable	**Coefficient (95% CI)**	***p***	**Coefficient (95% CI)**	***p***	**Coefficient (95% CI)**	***p***	**Coefficient (95% CI)**	***p***
Pain	-10.48 (-12.12, -8.92)	**<0.001**	-0.17 (-0.19, -0.15)	**<0.001**	-8.90 (-10.72, -7.08)	**<0.001**	8.07 (7.17, 8.97)	**<0.001**
Shortness of breath	-8.23 (-10.13, -6.42)	**<0.001**	-0.08 (-0.10, -0.06)	**<0.001**	-6.42 (-8.50, -4.35)	**<0.001**	6.32 (5.22, 7.43)	**<0.001**
Weakness	-12.85 (-14.35, -11.18)	**<0.001**	-0.12 (-0.14, -0.10)	**<0.001**	-10.47 (-12.39, -8.56)	**<0.001**	8.73 (7.78, 9.69)	**<0.001**
Nausea	-8.75 (-11.13, -6.65)	**<0.001**	-0.11 (-0.14, -0.08)	**<0.001**	-6.21 (-8.79, -3.63)	**<0.001**	9.10 (7.78, 10.42)	**<0.001**
Vomiting	-6.66 (-9,86, -3.80)	**<0.001**	-0.07 (-0.13, -0.03)	0.002	-2.96 (-7.34, 1.43)	0.186	8.98 (6.80, 11.16)	**<0.001**
Poor appetite	-9,57 (-12.82, -5.86)	**<0.001**	-0.11 (-0.16, -0.07)	**<0.001**	n/a	n/a	8.13 (6.33, 9.92)	**<0.001**
Constipation	-5.02 (-6.88, -3.37)	**<0.001**	-0.07 (-0.10, -0.04)	**<0.001**	-3.65 (-5.86, -1.43)	**0.001**	5.25 (4.14, 6.35)	**<0.001**
Sore or dry mouth	-6.03 (-8.08, -3.90)	**<0.001**	-0.09 (-0.11, -0.06)	**<0.001**	-4.20 (-6.72, -1.67)	**0.001**	6.24 (4.99, 7.50)	**<0.001**
Drowsiness	-10.21 (-13.20, -7.05)	**<0.001**	-0.10 (-0.13, -0.06)	**<0.001**	n/a	n/a	7.73 (5.98, 9.48)	**<0.001**
Poor mobility	-11.28 (-12.62, -9.95)	**<0.001**	-0.15 (-0.17, -0.14)	**<0.001**	-9.99 (-11.49, -8.51)	**<0.001**	7.63 (6.84, 8.43)	**<0.001**
Diarrhoea	-6.35 (-9,04, -3.52)	**<0.001**	-0.07 (-0.10, -0.03)	**<0.001**	-4.59 (-7.54, -1.65)	0.002	5.85 (4.29, 7.40)	**<0.001**
Tingling	-6.22 (-7.99, -4.52)	**<0.001**	-0.06 (-0.08, -0.04)	**<0.001**	-5.68 (-7.62, -3.74)	**<0.001**	4.22 (3.14, 5.29)	**<0.001**
Difficulty remembering	-7.41 (-9.30, -5.70)	**<0.001**	-0.09 (-0.11, -0.06)	**<0.001**	-4.74 (-7.00, -2.48)	**<0.001**	6.54 (5.26, 7.64)	**<0.001**
Anxiety	-9.56 (-11.27, -7.83)	**<0.001**	-0.12 (-0.14, -0.10)	**<0.001**	-8.89 (-10.79, -6.99)	**<0.001**	8.92 (8.13, 9.64)	**<0.001**
Depression	-10.34 (-12.15, -8.59)	**<0.001**	-0.14 (-0.17, -0.12)	**<0.001**	-8.26 (-10.50, -6.01)	**<0.001**	9.25 (8.24, 10.25)	**<0.001**
EORTC Physical function	-		-		-		-0.37 (-0.41, -0.34)	**<0.001**
EORTC Role Function	-		-		-		-0.29 (-0.31, -0.26)	**<0.001**
EORTC Social function	-		-		-		-0.30 (-0.33, -0.27)	**<0.001**

Table S3. Bivariate associations of independent variables with the the outcomes a) MyPOS total palliative care concerns, b) EQ5D Index, d) Global health status (EORTC QLQ-C30), n = 557

N (%)	*High palliative care concerns*	*Low palliative care concerns*	p-value	*Low EQ5D Index*	*High EQ5D Index*	p-value	*Low global QOL*	*High global QOL*	p-value
Sociodemographic details									
Age (years) Mean (SD)	66.2 (11.4)	69.4 (9.8)	**0.001**	67.7 (10.6)	69.1 (10.3)	0.109	68.4 (10.8)	68.2 (9.8)	0.892
Gender			0.441			0.029			0.129
Men	142 (30.3%)	151 (32.3%)		180 (32.7%)	158 (28.7%)		230 (41.4%)	113 (20.4%)	
Women	91 (19.4%)	83 (17.7%)		136 (24.7%)	74 (13.5%)		142 (25.6%)	68 (12.3%)	
Ethnicity			0.035			0.456			0.170
White background	211 (45.3%)	222 (47.6%)		296 (54.1%)	215 (39.3%)		343 (62.1%)	172 (31.2%)	
Non-white or mixed	22 (4.7%)	11 (2.4%)		20 (3.7%)	16 (2.9%)		28 (5.1%)	9 (1.6%)	
Marital status			0.188			0.061			0.037
Married	166 (35.3%)	171 (36.5%)		220 (40%)	174 (31.6%)		263 (47.4%)	136 (24.5%)	
Single, divorced, widowed	67 (14.3%)	61 (13%)		96 (17.5%)	55 (10%)		108 (19.5%)	43 (7.7%)	
Occupational status			0.049			**<0.001**			**<0.001**
Working	30 (6.4%)	44 (9.4%)		31 (5.7%)	51 (9.3%)		39 (7.1%)	43 (7.8%)	
Not working	203 (43.6%)	189 (40.6%)		285 (52.2%)	179 (32.8%)		332 (60.3%)	137 (24.9%)	
Disease factors									
Phase of illness			**<0.001**			0.136			**<0.001**
Newly diagnosed	47 (10.1%)	40 (8.6%)		55 (10.1%)	46 (8.4%)		75 (13.6%)	27 (4.9%)	
Stable phase	94 (20.2%)	135 (29%)		145 (26.5%)	119 (21.8%)		158 (28.6%)	109 (19.7%)	
Relapsed/progressive	92 (19.7%)	58 (12.4%)		116 (21.2%)	66 (12.1%)		138 (25%)	45 (8.2%)	
ISS stage at diagnosis			0.266			0.965			0.163
ISS stage I	68 (21%)	66 (20.4%)		87 (23%)	66 (17.4%)		99 (26%)	54 (14.2%)	
ISS stage II	41 (12.7%)	54 (16.7%)		62 (16.4%)	46 (12.1%)		66 (17.3%)	43 (11.3%)	
ISS stage III	52 (16%)	43 (13.3%)		69 (18.2%)	49 (12.9%)		86 (22.6%)	33 (8.7%)	
MM disease duration Mean (SD)	41.7 (43)	41.8 (38.1)	0.977	41.9 (40.6)	42.6 (40.9)	0.842	40.7 (40.5)	45.8 (41.3)	0.196
Type of myeloma			0.233			0.087			0.084
Light chain	43 (9.7%)	37 (8.3%)		60 (11.5%)	33 (6.3%)		69 (13.1%)	26 (5%)	
IgG or IgA	177 (39.8%)	188 (42.2%)		240 (46.2%)	187 (36%)		278 (53%)	152 (29%)	
Treatment factors									
Receiving treatment			**<0.001**			0.462			**<0.001**
Yes	140 (30%)	103 (22.1%)		168 (30.7%)	121 (22.1%)		216 (39.1%)	74 (13.4%)	
No	93 (20%)	130 (27.9%)		148 (27.1%)	110 (20.1%)		155 (28.1%)	107 (19.4%)	
Lines of treatment Median (IQR)	1 (1 – 2)	2 (1 – 3)	0.015	2 (1-2)	1 (1-2)	0.291	2 (1 – 2)	1 (1 – 2)	0.072

N (%)	*High palliative care concerns*	*Low palliative care concerns*	p-value	*Low EQ5D Index*	*High EQ5D Index*	p-value	*Low global QOL*	*High global QOL*	p-value
Treatment phase			0.014			0.239			0.004
Newly diagnosed	9 (1.9%)	17 (3.6%)		13 (2.4%)	16 (2.9%)		15 (2.7%)	15 (2.7%)	
First line treatment	54 (11.6%)	39 (8.4%)		67 (12.2%)	45 (8.2%)		85 (15.4%)	27 (4.9%)	
First treatment-free interval	46 (9.9%)	73 (15.7%)		72 (13.2%)	62 (11.3%)		78 (14.1%)	59 (10.7%)	
Second line treatment	28 (6%)	25 (5.4%)		38 (6.9%)	29 (5.3%)		50 (9.1%)	16 (2.9%)	
Second treatment-free interval	34 (7.3%)	35 (7.5%)		59 (10.8%)	28 (5.1%)		62 (11.2%)	26 (4.7%)	
Later phase	62 (13.3%)	44 (9.4%)		67 (12.2%)	51 (9.3%)		81 (21.8%)	38 (6.9%)	
Functional and symptom status									
ECOG performance status			**<0.001**			**<0.001**			**<0.001**
0 – Fully active	51 (11.1%)	111 (24.1%)		59 (10.9%)	126 (23.3%)		81 (14.9%)	107 (19.6%)	
1 – Restricted	84 (18.3%)	103 (22.4%)		134 (24.8%)	84 (15.6%)		157 (28.8%)	64 (11.7%)	
2 – Unable to work	56 (12.2%)	12 (2.6%)		74 (13.7%)	13 (2.4%)		81 (14.9%)	5 (0.9%)	
3/4 – Limited self care, confined to bed	38 (8.3%)	5 (1.1%)		45 (8.3%)	5 (0.9%)		46 (8.4%)	4 (0.7%)	
Number of symptoms			**<0.001**			**<0.001**			**<0.001**
0	0	5 (1.1%)		0	5 (0.9%)		0	5 (0.9%)	
1-5	13 (2.8%)	135 (28.9%)		37 (6.8%)	135 (24.7%)		53 (9.6%)	122 (22.1%)	
6-8	67 (14.3%)	74 (15.8%)		109 (20%)	58 (10.6%)		127 (23%)	39 (7.1%)	
9-15	152 (32.5%)	21 (4.5%)		170 (31.1%)	32 (5.9%)		191 (34.7%)	14 (2.5%)	

Bonferroni correction used per outcome variable, critical alpha level <0.003

ECOG: Eastern Cooperative Oncology Group performance status, IQR: Interquartile range, ISS: International Staging system for multiple myeloma [24], SD: standard deviation

Erratum

Erratum to: The impact of disease-related symptoms and palliative care concerns on health-related quality of life in multiple myeloma: a multi-centre study

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Erratum

Unfortunately, the original version of this article [1] contained an error. In Table 3, Outcome data scores for total sample and comparison of symptoms and palliative care needs across disease phases, there was an error in the calculation of the EORTC QLQ-MY20 subscale "Disease symptoms" and "Side-effects of treatment". In both cases, the printed mean and median values of both subscales are too high. These two symptom subscales were erroneously calculated using the syntax for functioning subscales. The corrected mean and median values for "Disease symptoms" and "Side-effects of treatment" for the complete sample and the three subgroups of newly diagnosed, treatment-free interval / stable disease and progressive, relapsed disease have been corrected in Table 3 (see corrected version below, corrections are in red).

Table 3. Outcome data scores for total sample and comparison of symptoms and palliative care needs across disease phases

	Score			Newly diagnosed (n=102)			Treatment-free interval / stable disease (n=268)			Progressive, relapsed stage (n=184)			Test	
Measure	n	Mean, SD	Median (range)	n	Mean, SD	Median (range)	n	Mean, SD	Median (range)	n	Mean, SD	Median (range)	F value	p
Time since diagnosis (months)	552	42.3 (40.7)	29.9 (0.1-283)	102	10.4 (16.8)	4.6 (0.2-103.1)	267	44.2 (39.8)	30.4 (0.49-239.9)	183	57.3 (41.8)	57.3 (41.8)	52.2	**0.001**
ECOG Performance status	551	-	1 (0-4)	101	-	1 (0-3)	268	-	1 (0-4)	182	-	1 (0-4)	X^2: 24.4	**0.002**
MyPOS[a]														
Total score	468	21.5 (13.5)	19 (0-61)	86	22.9 (13.4)	20 (1-61)	229	18.9 (13.1)	17 (1-59)	150	24.7 (13.4)	23 (0-61)	9.6	**0.001**
Symptoms and function	526	76.2 (16.6)	78.8 (30.4-100)	96	75.8 (14.5)	76.8 (36-100)	253	79.1 (14.3)	80.4 (30.4-100)	175	72.2 (14.8)	71.4 (34-100)	11.9	**0.001**
Emotion and coping	499	80 (16.6)	84.4 (18.8-100)	94	77.1 (17.2)	81.3 (34-100)	244	82.4 (16.2)	87.5 (18.8-100)	158	77.9 (16.4)	81.3 (34-100)	5.3	**0.005**
Healthcare support and information needs	544	90.8 (12.7)	95 (40-100)	99	91.2 (12.8)	95 (40-100)	264	91.1 (12.9)	100 (40-100)	178	89.8 (12.5)	95 (50-100)	0.6	0.532
EORTC-QLQ-C30[b]														
Global health status	555	61.2 (22.3)	66.7 (0-100)	102	59.5 (20.5)	66.7 (0-100)	267	65.8 (21.8)	66.7 (0-100)	183	55.2 (22.7)	50 (0-100)	12.9	**0.001**
Physical function	554	61.5 (22.5)	60 (0-100)	101	61.2 (26.7)	66.7 (0-100)	266	65.3 (25.2)	66.7 (0-100)	184	56.2 (24.6)	53.3 (0-100)	6.9	**0.001**
Role function	553	59 (33.1)	66.7 (0-100)	101	55.4 (35.6)	66.7 (0-100)	266	64.9 (30.9)	66.7 (0-100)	183	52.3 (33.5)	50 (0-100)	8.9	**0.001**
Emotional function	555	76.2 (22.1)	83.3 (0-100)	102	74.5 (23.7)	83.3 (0-100)	267	77.3 (21.3)	83.3 (0-100)	183	75.3 (22.3)	75 (0-100)	0.8	0.459
Cognitive function	555	79 (21.9)	83.3(0-100)	102	78.1 (21.9)	83.3 (0-100)	267	81.2 (20.5)	83.3 (16.7-100)	183	76.3 (23.7)	83.3 (0-100)	2.8	0.060
Social function	554	65.1 (31.5)	66.7 (0-100)	102	60.5 (34.8)	66.7 (0-100)	267	70.2 (29.3)	66.7 (0-100)	182	60.1 (31.7)	66.7 (0-100)	7.1	**0.001**
EORTC QLQ-MY20[c]														
Disease symptoms	549	26.0 (21.2)	22.2 (0-100)	101	24.3 (20.9)	22.2 (0-100)	262	26 (20.9)	22.2 (0-94.4)	183	27.3 (21.8)	22.2 (0-100)	0.6	0.530
Side-effects of treatment	542	18.6 (14.4)	16.7 (0-100)	100	19.7 (14)	16.7 (0-56.7)	261	16.4 (14)	13.3 (0-70)	178	21.2 (14.9)	20 (0-76.7)	6.1	**0.002**
Body image	551	77.9 (30.5)	100 (0-100)	100	79 (31.7)	100 (0-100)	265	79.6 (28.2)	100 (0-100)	183	74.9 (32.8)	100 (0-100)	1.4	0.247
Future perspective	549	64.6 (26.5)	66.7 (0-100)	100	61.4 (28.1)	66.7 (0-100)	264	67.2 (25.1)	77.8 (0-100)	182	62.1 (27.3)	66.7 (0-100)	2.8	0.061

EuroQOL-5D-3L														
EQ5D Index score	550	0.65 (0.28)	0.69 (-0.5 – 1)	101	0.66 (0.28)	0.69 (-0.18 – 1)	264	0.67 (0.27)	0.69 (-0.18 – 1)	182	0.59 (0.29)	0.69 (-0.35 – 1)	4.5	**0.012**
EQ5D Visual analogue scale VAS	318	63.51 (20.02)	61 (0.5 – 100)	68	58.8 (19.8)	60 (0.5 – 96)	139	69 (19.6)	69.5 (11 – 100)	111	59.5 (19.1)	60 (10 – 100)	9.82	**0.001**

[a]MyPOS: Myeloma Patient Outcome Scale: comprises 27 items with 11 symptoms and 16 myeloma-specific palliative care needs, total maximum possible score 65, higher scores indicate higher symptom burden/more palliative care needs, MyPOS subscale scores transformed to 0-100 scale to allow for comparison to subscale scores from the EORTC QLQ-C30 and –MY20 questionnaires.
[b]EORTC QLQ-C30: For the EORTC-QLQ-C30, higher scores on functioning subscales and the global quality of life scale indicate better functioning/better quality of life.
[c]EORTC-QLQ-MY20: For the myeloma module of the EORTC quality of life questionnaire, higher scores indicate more problems/symptoms in symptom subscales and lower problems in functioning subscales.

References

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6 Results: Longitudinal trajectories of quality of life in multiple myeloma and predictive factors

In this chapter, I present the longitudinal trajectories of symptom burden and quality of life in multiple myeloma, based on five measurement time points over a period of eight months. The primary aim of this study was to identify the intra-individual change trajectories of quality of life among multiple myeloma patients at various stages of disease over a period of 8 months.

It was hypothesised that four or five different trajectories of QOL would be found.

Hypothesis 1a: It was expected to find classes with stable QOL; low, moderate or high. It was assumed that some patients would experience a stable, good QOL, and others would experience moderate or poor levels of QOL throughout the observation period, which would be chronic.

Hypothesis 1b: Classes with changes in QOL level – either improving or deteriorating QOL – were expected.

The second aim was to evaluate whether the general symptom level and demographic as well as clinical characteristics help determine in particular those with a deteriorating QOL or chronic poor QOL trajectory.

Hypothesis 2a: It was expected that a high symptom burden along with a later/more advanced disease stage, a higher comorbidity level and a lower ECOG performance status would predict inclusion in classes with poor or deteriorating QOL trajectories.

Hypothesis 2b: It was hypothesised that the high symptom burden would act as a mediator in predicting inclusion in trajectories of poor chronic or deteriorating QOL.

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Symptoms and anxiety predict declining health-related quality of life in multiple myeloma: A prospective, multi-centre longitudinal study

Short title: Symptoms predict declining quality of life in multiple myeloma

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Abstract

Objective: To identify which patients might benefit from early integration of palliative care, by identifying trajectories of health-related quality of life (HRQOL) and symptoms over time, and determining which demographic and clinical characteristics predict declining or poor HRQOL.

Design: Prospective, longitudinal cohort study.

Setting: Inpatient and outpatient haematological or chemotherapy units at 14 hospitals in England.

Participants: Multiple myeloma at all stages (newly diagnosed, first line or second line treatment, early or later treatment-free interval, refractory disease).

Main Outcome Measure: In addition to demographic, clinical, treatment information and standardised HRQOL and psychological aspects, the Myeloma Patient Outcome Scale (MyPOS) measured palliative care concerns.

Results: Between February and August 2013, 238 patients were recruited, on average 3.5 years (SD: 3.4) post-diagnosis. Latent mixture growth models identified four HRQOL trajectories. Classes 3 and 4 represent trajectories of stable poor HRQOL or declining HRQOL over an eight months period. The strongest predictors of poor outcome at the end of follow-up were general symptom level (OR: 1.3, 95% CI: 1.0 to 1.6, p = 0.028), presence of clinically relevant anxiety (OR: 1.2, 95% CI: 1.0 to 1.4, p = 0.019), and presence of pain (OR: 1.02, 95% CI: 1.0 to 1.1, p = 0.018), all being more predictive than demographic or clinical characteristics.

Conclusion: General symptom level, pain and presence of anxiety predict declining HRQOL in multiple myeloma. Identification of patients with palliative care needs should focus on assessing patient-reported symptoms and psychosocial well-being for identifying those at risk of deterioration.

Keywords: Multiple myeloma, Health-related quality of life, Palliative Care Outcome Scale, Symptom burden, Quality of life, Palliative care

Introduction

Due to the ageing of populations and the rising incidence of cancer, health care systems will face a growing number of people at the end of life in need of palliative care. The WHO estimates that around 8 million people die of cancer worldwide, of which a substantial number will have palliative care needs [1]. With treatment options and the introduction of novel anti-cancer agents, the lives of cancer patients have been lengthened, which in turn has changed the cancer trajectory, resulting in chronic disease patterns. This changing face of cancer has also altered the role of palliation and specialist palliative care (SPC) services are now advocated to be integrated with treatment of curative intent [2-4].

One such cancer is multiple myeloma (MM), an incurable haematological malignancy of the bone marrow and one of the most common haematological cancers with incidences of 3.29 to 4.82 per 100,000 population [5,6]. MM is primarily a disease of older age with a median age at time of diagnosis of 73 years and almost 40% of patients being 75 years or older [7,8]. This has implications for treatment options and survival time, as the most intense options such as stem cell transplantation are only accessible to younger patients. Myeloma results in bone destruction, bone marrow failure and renal impairment [9]. Throughout their disease trajectory, patients suffer from a variety of symptoms, some resulting from advancing disease, some being treatment side effects such as neuropathies [10]. There is evidence that myeloma patients suffer more symptoms and problems than other cancers [11]. Unlike solid cancers, where relatively high levels of functioning are maintained up until a distinct and short period of terminal decline [12], haematological malignancies often follow no such clear pattern. Trajectories rather show entry, re-entry characteristics, with periods of intensive antineoplastic regimens that may continue until the end of life, hospitalisations due to treatment complications, interspersed with stable, treatment-free intervals [13-15]. Death follows a period of rapid decline or arrives suddenly during exacerbations [16,17]. These characteristics make determination of palliative status and referral to SPC difficult in this patient group. Indeed, haematologists in Australia and the UK have expressed insecurities regarding when referral is appropriate [17,18].

Therefore, haematological cancer patients still miss out on SPC, as evidenced by a meta-analysis showing that the number of referrals to SPC is much lower in this cancer group than in solid tumours [19]. A meta-analysis investigating place of death (often used as a proxy for quality of end of life care) in haematological cancers showed that patients with a haematological cancer have 2.25 times the odds of dying in hospital [20,21]. Even if SPC is initiated, it is often done too late in the disease trajectory [20,21]. However, early integration of palliative care as a new model can only be achieved by knowing which patients are in need of such receipt of care. Several prognostic indicators for predicting patient survival and therefore initiation of palliative care have

been developed, based on clinical features, laboratory data, and response to treatment [22-24]. However, one of the most interesting findings in recent years has been the evidence for the independent prognostic role of patient-reported outcomes [25]. Patient's experience of disease, symptoms and treatment-related side effects can provide clinically meaningful information on prognosis in multiple myeloma [26-28]. This could help identify those with poor quality of life (QOL) that would benefit from early palliative care involvement.

In this study we sought to determine (a) how symptoms common in multiple myeloma and HRQOL change over time, (b) what demographic and clinical characteristics predict declining health-related quality of life. Specifically, it was hypothesised that we would identify four or five different trajectories of QOL, characterised by stability or fluctuation and the initial level of QOL that was experienced by patients (good, moderate or poor HRQOL). It was also expected to find classes of QOL experiences with either an improving or a deteriorating QOL course. It was further expected that a high symptom burden together with a more advanced disease stage, higher comorbidity level and a lower Eastern Cooperative Oncology Group (ECOG) performance status would predict inclusion in classes with poor or deteriorating QOL.

Methods

For this multi-centre, longitudinal prospective study, patients with multiple myeloma were recruited from both inpatient stem cell transplantation units and outpatient haematology clinics or chemotherapy day care centres in 14 secondary and tertiary hospitals in England, United Kingdom, from February to August 2013. The study protocol and procedures were approved by the Central London Research Ethics Committee (study ref number: 13/LO/1140). Further local Research and Development approvals were obtained from all 14 participating NHS hospital trusts. The study was conducted according to the principles expressed in the Declaration of Helsinki. All participants were given full information regarding the study, signed to indicate their consent, and could withdraw at any time without giving reasons or withdrawal affecting their medical treatment. All information was kept confidential.

Participants and procedures

Consecutive patients were screened by a member of the clinical team for eligibility according to study entry criteria at all the participating sites. Eligibility criteria were designed to identify people at various stages of their disease rather than focusing on a cohort at the end-of-life. Eligibility criteria were: adult patients with confirmed diagnosis of multiple myeloma that had been disclosed to the patient, and capacity to give informed written consent. Patients who were

too unwell, distressed or symptomatic to participate were excluded, as were patients with severe neutropenia or for whom myeloma was not the most important health problem.

All patients screened eligible were asked permission by the clinical staff to being approached by a study nurse or research assistant, who explained the study and obtained written consent. At this point the research nurse or researcher also completed the demographic information sheet. The study questionnaires were either completed during the clinic visit or at home with patients being supplied a pre-paid envelope for returning the questionnaire to the institute. Subsequent questionnaires were sent via mail to patients, with a pen, a sweet and a self-addressed, pre-stamped envelope provided for return. Participants received one written reminder and an additional second telephone reminder if they did not return their questionnaire within two weeks. Patients were followed, if possible, if they moved to a nursing home, hospital, or hospice. We sought information about any deaths that occurred.

Among the disease details, the date of diagnosis and the immunoglobulin type (Ig) were extracted, alongside time since diagnosis and stage according to the International Staging System (ISS) [29]. The current phase of illness was classified as newly diagnosed (pre-treatment or undergoing first-line treatment), stable disease (watch and wait or receiving maintenance treatment with no evidence of disease progression) or relapsed/progressive disease (second line therapy or above, lack of response or progression on treatment or receiving palliative care) [30]. Treatment details were recorded [22].

Measurements

Participants were followed up for a period of eight months from baseline. They completed postal surveys every two months for a total of five assessments. Questionnaires that were administered assessed their generic or disease-specific QOL and symptom burden – the Myeloma Patient Outcome Scale MyPOS [31], the European Organisation for the Research and Treatment of Cancer (EORTC) QLQ-C30 [32] and its myeloma module MY20 [33]; the Hospital Anxiety and Depression Scale for measuring depression and anxiety [34], and a mastery of illness scale [35]. Comorbidities [36] and performance status [37] was also assessed directly from the patient. Table 1 presents a short description of each outcome measure. The MyPOS is shown in Figure S1. The MyPOS and the symptom list within the EORTC QLQ-C30 and QLQ-MY20 were used to assess general symptom level and 15 common symptoms in myeloma [39]: pain, bone pain, weakness, drowsiness, breathlessness, nausea, vomiting, constipation, diarrhoea, sore/dry mouth, poor mobility, tingling in the hands/feet, problems remembering, sleeplessness, and poor mobility. If these symptoms were scored mild/moderate to extreme severe/severely on the instruments, they were coded as ‘present’ and added to form a general symptom level score. This score was further categorised as low (1-5 symptoms), moderate (6-8 symptoms) and high (9-15 symptoms).

Table 1. Data collection and questionnaires for outcome collection

	Measure	Description and scoring
Symptom status and palliative care problems	MyPOS [31]	33-item questionnaire with 15 disease- and treatment-specific symptoms, 13 myeloma-specific quality of life items, 5 generic items about palliative care concerns Module of Palliative Care Outcome Scale [41] Three subscales: Functioning and symptoms, Emotional response, Healthcare support (information and satisfaction with care) 5-point Likert scale (0 – not at all to 4 – overwhelming) Possible range of 0-132 for total score (higher score means more symptoms/problems)
Health-related quality of life	EORTC QLQ-C30 [32]	30-item generic health-related quality of life questionnaire Five functional scales (physical, role, emotional, social, cognitive functioning), six symptom scales (fatigue, nausea/vomiting, pain, dyspnoea, constipation, appetite loss, sleeping problems, financial difficulties), one global health status/ quality of life scale 4-point Likert scale (1 – not at all to 4 – Very much), except for two 7-point global health status/quality of life items Transformation of all scales to 0-100 scale (41) High scores on functional scales and global quality of life scales represent high level of functioning/quality of life High scores on symptom scales represent a high symptom burden
	EORTC-QLQ-MY20 (33)	20-item add-on module of disease-specific symptoms and functional impact for multiple myeloma, added onto the EORTC-QLQ-C30 Two symptom subscales (disease symptoms and side-effects of treatment), two functional subscales (body image and future perspectives) 4-point Likert scale (1 – not at all to 4 – Very much) Transformation of all scales to 0-100 scale High scores on functional scales represent high levels of functioning. High scores on symptom scales represent a high symptom burden.
Psychological status	Hospital Anxiety and Depression Scale (HADS) (34)	14-item measure to diagnose depression and anxiety in non-psychiatric hospital samples. Depression and anxiety subscale consist of 7 items each 4-point Likert scale from 0 (no problem) to 3 (maximum distress) Range of total score from 0 to 21 on each subscale. Cut-offs for the presence of clinically relevant anxiety or depression defined as ≥ 8 on each subscale (42,43)
Mastery of illness	Global Mastery Scale (35)	7-item scale to measure the impact of disease and treatment on perception of self and perceived control/mastery over illness 5-point Likert scale ranging from 1 (strongly disagree) to 5 (strongly agree) 4 items need to be reversed scored to form a total score of 35.

Statistical analysis

In order to detect a difference between subgroups in an independent, two-tailed t-test with 80% power, at a significance level of 5% and assuming a moderate effect size of 0.5-0.6 of change on the total MyPOS score, the estimated total sample size is 64 to 90. Allowing for attrition of 25-30% over the course of one year, 113-117 patients needed to be recruited to the study.

Descriptive statistics (mean, standard deviation, percentages, medians and interquartile ranges for categorical data) were calculated. Prevalence of symptoms over time was determined as point prevalence with 95% confidence intervals at each time point. Objective 1, determining change in QOL over time was established via latent class growth analysis (LGCA) [44]. Repeated measures of a continuous variable are used to identify classes with a categorical latent variable that represent homogeneous subgroups within the sample [44]. A trajectory class thus consists of a group of patients sharing a common course of HRQOL. The outcome that was modelled was the total MyPOS score for each patient. LGCA analysis follows several analytical steps [45]: First, different growth functions (linear, quadratic, piecewise) for modelling general slope growth were tested in a growth model without classes, to test which growth function would provide the best fit to the data. Second, the optimal number of classes was tested with within-class variance on growth parameters (slope) freely estimated [45]. Decisions on the number of classes of HRQOL trajectories were based on fit indices, in combination with clinical interpretability of the classes [46]. The mean class trajectories of the total MyPOS scores and all individual patient trajectories were plotted for each graph.

To identify predictors for poor HRQOL, we ran ordinal logistic regression models with the proportional odds assumption. A poor HRQOL outcome was defined as reporting a low level of HRQOL throughout the study period or reporting deteriorating MyPOS scores over the eight months period, based on the classes of HRQOL trajectories found in the latent class growth modelling. We first tested bivariate associations between the outcome variable and potential predictors (including demographic, clinical information, general symptom level and psychological symptoms) using nominal regression. Those predictors found to be significant at the 0.2 level in bivariate analyses were included in multivariable models.

The main analysis included non-missing data only. Missing data in LGCA were addressed using Full Information Maximum Likelihood (FIML) [47]. Regression analyses were repeated on multiple imputed data for sensitivity analyses. Three methods of imputation were used: (a) last observation carried forward (LOCF), (b) imputation of the median value for each single item, stratified by disease stage of the individual, and (c) multiple imputation [48]. Results from

sensitivity analyses are reported in Table S4. All analyses were conducted using SPSS v22 [49], except for LGCA which was conducted in MPlus 7.31 [50]. All statistical tests used a 0.05 two-tailed alpha level of significance.

Results

Demographic and clinical characteristics

The mean age of the sample was 68.5 (SD 10.5), with 87 women (36.6%) and with an average disease duration of 39 months (0 to 24 years, 95% CI: 34.2 – 44.1). A quarter of patients had lived longer than 5 years with myeloma (20.6%). According to phase of illness, most were in a stable or plateau phase (53.1%). 48.7% were in a later treatment phase, receiving second line treatment or higher with 35.7% having received at least two lines of treatment. According to the ECOG performance status, one quarter had at least moderate to severe disability – with 20.2% being unable to work or bedridden. The mean Charlson Comorbidity index was 4.9 (95% CI: 4.7 – 5.1). Clinical characteristics are shown in Table 2.

Table 2. Demographic, clinical and treatment characteristics of 238 multiple myeloma patients

Variables	238 MM patients
Age (years), *mean (SD)*	68.5 (10.5)
Men, *N(%)*	147 (61.8)
Married, *N(%)*	170 (71.4)
White, *N(%)*	220 (92.4)
Education level, *N(%)*	
Secondary school	137 (57.5)
Technical qualification	52 (21.8)
University	41 (17.3)
Working, *N(%)*	41 (17.2)
Type of myeloma, *N(%)*	
IgA or IgG	180 (78.6)
Light chain disease	39 (16.4)
Other	9 (3.8)
ISS stage at diagnosis, *N(%)*	
I	68 (28.6)
II	41 (17.2)
III	52 (18.6)
Time since diagnosis (in months), *mean (SD)*	39.1 (38.2)
Disease stage, *N(%)*	
Newly diagnosed	38 (15.9)
Stable/plateau	128 (53.8)
Relapsed/progressive/refractory disease	72 (30.3)
Treatment phase, *N(%)*	
Newly diagnosed	3 (1.3)
First-line treatment*	35 (14.7)
First treatment-free interval*	79 (33.2)
Second-line treatment	31 (13.0)
Second treatment-free interval	41 (17.2)
Later phase	49 (20.6)
Currently receiving treatment, *N(%)*	118 (49.6)

Active therapy	80 (33.6)
Maintenance therapy	38 (15.9)
Current MM treatment, *N(%)*	
Bortezomib or Carfilzomib	46 (19.3)
Lenalidomide	48 (20.2)
Thalidomide/Pomalidomide	27 (11.3)
Alkalyting agent (Cyclophosphamide, Melphalan, Bendamustine, Vincristine)	45 (18.9)
High-dose steroids	73 (30.7)
Other (Interferon, Situximab, Fluradabine, Vorinostat)	9 (3.8)
Those with current treatment receiving combination therapy	70 (29.4)
Past MM treatment, *N(%)*	
Bortezomib or Carfilzomib	96 (40.3)
Thalidomide/ Lenalidomide/ Pomalidomide	179 (75.2)
Alkalyting agent	179 (75.2)
High-dose steroids	194 (81.5)
Doxorubicin	22 (9.2)
Other (Interferon, Situximab, Fluradabine, Vorinostat)	4 (1.7)
Bisphosphonates	105 (44.1)
Radiotherapy	31 (13.0)
Intensity of received treatments, *N(%)*	
Chemotherapy only	111 (46.7)
Chemotherapy and HSCT	76 (31.9)
Two or more HSCT	15 (6.3)
Lines of treatment received*, *mean (SD)*	1.5 (1.2)
ECOG performance status, *N(%)*	
0 Fully active	79 (33.2)
1 Restricted	104 (43.7)
2 Unable to work	33 (13.9)
3 or 4 – Limited self-care/bed-bound	15 (6.3)
Charlson comorbidity index, *mean (SD)*	4.9 (1.5)

ECOG: Eastern Cooperative Oncology Group performance status, HSCT: haematopoietic stem cell transplantation, IgA: Immunoglobulin A, IgG: Immunoglobulin G, ISS: International Staging System for multiple myeloma, ISS I: Serum β^2 microglobulin < 3.5 mg/L and Serum albumin ≥ 3.5 g/dL, ISS II: not ISS I or ISS III, ISS III: Serum β^2 microglobulin > 5.5 mg/L [29].
*Initial induction and HSCT were counted as one single line of treatment. Likewise, if during a line of treatment the anti-myeloma therapy was changed due to unresponsiveness or side effects, this was still counted as one line. If active treatment was followed by maintenance treatment, active and maintenance were counted as one line. A treatment-free interval was defined by not receiving active or maintenance anti-myeloma therapy, whereas supportive therapies (e.g. bisphosphonates or anti-anaemia treatment) were possible.

A total of 250 patients were recruited and consented into the study, with 238 patients completing questionnaires at baseline. 199 participants completed time point 2 (83.6%), 171 completed time point 3 (71.8%), 150 completed time point 4 (63%) and 125 (52.5%) completed the last time point 5 questionnaire. Of the 113 patients lost to follow-up, 9 had died, 17 had been feeling too unwell to continue with the study, 2 had moved, and 88 had given no reason to discontinue the study. 12 questionnaire had been lost in the mail (see Figure S2).

Prevalence of common symptoms over time

Table 3 presents the percentages of patients reporting each symptom as moderate, severe or overwhelming on the MyPOS and on the EORTC QLQ-C30/MY20 at each time point. At baseline, over half of patients reported fatigue (52.1%) and 40.3% reported moderate to overwhelming pain. One third of patients reported anxiety (31.1%). About one fourth of patients reported moderate to overwhelming breathlessness (20.2%), drowsiness (26.1%), Tingling in the hands or feet (26.1%) and sleeping problems (24.4%). The frequency of moderate to overwhelming symptoms subsequently decreased over time with an increase seen at the last assessment, 8 months post-baseline.

Table 3. Percentages of patients with symptoms at moderate to overwhelming levels across five time points

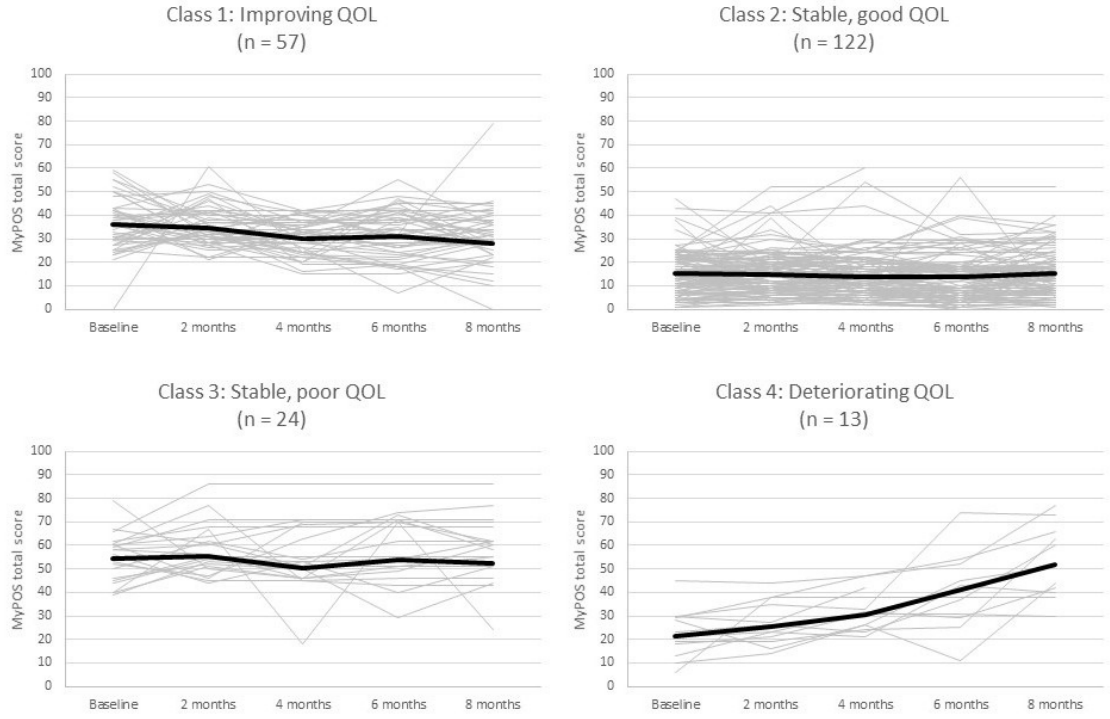
Symptom	Baseline (%)	2 months (%)	4 months (%)	6 months (%)	8 months (%)
Pain[a]	40.3 (34.1-46.5)	36.1 (30-42.2)	27.7 (22-33.4)	21.8 (16.6-27.1)	25.2 (19.7-30.7)
Bone pain[c]	67.7 (61.7-73.6)	58.0 (51.8-64.3)	48.3 (41.9-54.6)	39.9 (33.7-46.1)	39.8 (33.6-46.0)
Breathlessness[a]	20.2 (15.1-25.3)	21.8 (16.6-27.1)	18.5 (13.6-23.4)	16.8 (12.1-21.6)	16.8 (12.1-21.6)
Fatigue[a]	52.1 (45.8-58.5)	44.5 (38.2-50.8)	31.9 (25.9-37.8)	28.6 (22.9-34.3)	29.8 (24.0-35.6)
Nausea[a]	6.7 (3.5-9.9)	5.9 (2.9-8.9)	3.8 (1.4-6.2)	6.7 (3.5-9.9)	5.5 (2.6-8.4)
Vomiting[a]	3.8 (1.4-6.2)	1.7 (0.1-3.3)	0.8 (0-1.9)	1.7 (0.1-3.3)	1.3 (0.1-2.7)
Poor appetite[a]	16.8 (12.1-21.6)	15.5 (10.9-20.1)	9.7 (5.9-13.5)	9.7 (5.9-13.5)	10.5 (6.6-14.4)
Constipation[a]	18.5 (13.6-23.4)	16.8 (12.1-21.6)	10.5 (6.6-14.4)	9.2 (5.5-12.9)	11.8 (7.7-15.9)
Dry mouth[a]	18.9 (13.9-23.9)	14.3 (9.9-18.8)	12.6 (8.4-16.9)	8.4 (4.9-11.9)	11.3 (7.3-15.3)
Drowsiness[a]	26.1 (20.5-31.7)	26.1 (20.5-31.7)	16.8 (12.1-21.6)	16.8 (12.1-21.6)	14.7 (10.2-19.2)
Diarrhoea[a]	8.8 (5.2-12.4)	8.0 (4.6-11.5)	5.0 (2.2-7.8)	6.7 ((3.5-9.9)	5.0 (2.2-7.8)
Tingling in hands/feet[a]	26.1 (20.5-31.7)	22.3 (17-27.6)	18.1 (13.2-23.0)	14.7 (10.2-19.2)	16.4 (11.7-21.1)
Problems remembering[a]	19.7 (14.6-24.8)	19.3 (14.3-24.3)	16.0 (11.3-20.7)	12.2 (8.0-16.4)	10.1 (6.3-13.9)
Sleeping problems[b]	24.4 (18.9-29.9)	20.6 (15.5-25.8)	16.4 (11.7-21.1)	16.4 (11.7-21.1)	12.6 (8.4-16.9)
Poor mobility[a]	42.5 (36.2-48.8)	57.1 (50.8-63.4)	23.5 (18.1-28.9)	19.3 (14.3-24.3)	20.6 (15.5-25.8)

a Symptom taken from the MyPOS.
b Symptom taken from the EORTC QLQ-C30.
c Symptom taken from the EORTC QLQ-MY20.

Trajectories of quality of life in multiple myeloma

The adequacy of fit of several growth functions, including linear, piecewise, and quadratic growth factors was tested for each of the three QOL outcomes with the linear growth function providing the best fit in each model. Table S3 contains the fit indicators for the number of latent classes in QOL trajectories in LGCA analysis. Across the models, a 4-class and 5-class solution worked best with values for the BIC and AIC decreasing for these models compared to models with smaller or higher numbers of classes (see Table S3). Among the two, the BIC and entropy values as well as the Bootstrap Likelihood ratio test supported the four-class solution. The four-class solution was chosen based on the better BIC, entropy and likelihood test values, better clinical interpretability and better class group sizes than seen in the 5-class solution.

Figure 1 Four trajectories of HRQOL (MyPOS) (Solid line: Estimated unadjusted mean growth curve; grey line: individual trajectories)



216 participants contributed enough data at all time points to enter trajectory analysis. Figure 1 shows the four trajectories of QOL and palliative care concerns. The first trajectory (n=57, 26.4%) followed a pattern of slightly improving QOL, with an initial medium level of symptoms and problems (*M* = 36.7, *SD* = 10.8 at T1), and subsequently decreasing over 8 months to a lower level of symptoms (*M* = 28.6, *SD* = 10.1 at T5). Most of the sample (n=122, 56.5%) fell under a pattern of stable, good QOL, starting from an already high QOL baseline level at T1 (*M* = 14.9, *SD* = 7.6) and showing only minute differences over the 8 months follow-up (*M* = 15.1, *SD* = 8.5 at T5). The third class (n = 24, 11.1%), termed stable, poor QOL, was characterised by generally high symptom burden/palliative care concerns throughout the follow-up period (*M* = 55.1, *SD* =

9.9 at T1 to *M* = 53.1, *SD* = 13.5 at T5) and experiencing a much lower baseline QOL than all other classes. In the fourth class (n = 13, 6%), termed deteriorating QOL, participants experienced relatively medium initial levels of QOL (*M* = 20.6, *SD* = 8.4 at T1) with subsequent stark decreases in QOL, particularly from T3 to T5 (*M* = 54.9, *SD* = 12.3 at T5).

Sample characteristics of MyPOS trajectories

Table 4 presents the demographic and clinical characteristics of participants per MyPOS trajectory class. Multinomial regression models showed significant associations between trajectory class and the demographic factors occupational status and the clinical characteristics ECOG performance status and intensity of prior treatments. More participants in class 1, slightly improving QOL, and class 2, stable good QOL, were working when comparing observed with expected frequencies. Participants with a trajectory of poor or deteriorating QOL (classes 3 and 4) were experiencing a poorer ECOG performance status, but had less intensive treatments than expected, compared to members of other classes.

Table 4. Multinomial logistic regression analysis of sample characteristics (demographic, clinical variables) and MyPOS trajectory classes (*N*=238)

Variable	Improving QOL (*n*=57)	Stable good QOL (*n*=122)	Stable poor QOL (*n*=24)	Deterio-rating QOL (*n*=13)	X^2	*p* value
Age (years), mean (SD)	64.8 (11.3)	69.7 (10.1)	67.1 (11.5)	71.9 (6.3)	138.5	.401
Men, *N(%)*	36 (63.2)	82 (67.2)	13 (54.2)	6 (46.2)	3.7	.298
Married, *N(%)*	46 (80.7)	87 (71.3)	16 (66.7)	9 (69.2)	2.9	.409
White, *N (%)*	50 (87.7)	114 (93.4)	22 (91.7)	13 (100)	3.7	.292
Education level, *N(%)*					11.3	.501
Secondary school	28 (7)	63 (51.6)	16 (66.7)	10 (76.9)		
Technical qualification	12 (21.1)	29 (23.8)	5 (20.8)	3 (23.1)		
University	11 (19.3)	26 (21.3)	2 (8.3)	0 (0)		
Working, *N(%)*	**12 (21.1)**	**24 (19.7)**	**2 (8.3)**	**0 (0)**	**7.7**	**.049**
Disease stage, *N(%)*					6.5	.365
Newly diagnosed	13 (22.8)	13 (10.7)	2 (8.3)	1 (7.7)		
Stable/plateau	26 (45.6)	73 (59.8)	14 (58.3)	8 (61.5)		
Progressive/palliative disease	17 (29.8)	34 (27.9)	8 (33.3)	4 (30.8)		
Type of myeloma, *N(%)*					6.5	.689
IgA or IgG	40 (70.1)	92 (75.5)	20 (83.3)	12 (92.3)		
Light chain disease	10 (17.5)	21 (17.2)	3 (12.5)	1 (7.7)		
Other	4 (7)	4 (3.3)	0 (0)	0 (0)		
ISS stage at diagnosis, *N(%)*					7.7	.262
I	12 (21.1)	38 (31.1)	8 (33.3)	1 (7.7)		
II	11 (19.3)	22 (18)	2 (8.3)	4 (30.8)		
III	13 (22.8)	25 (20.5)	7 (29.2)	4 (20.8)		

ECOG performance status, *N(%)*					**43.7**	**.000**
0 Fully active	15 (26.3)	50 (41)	3 (12.5)	6 (46.2)		
1 Restricted	25 (43.9)	61 (50)	6 (25)	3 (23.1)		
2 Unable to work	13 (22.8)	6 (4.9)	7 (29.2)	2 (15.4)		
3/4 limited self-care or bedbound	2 (3.5)	3 (2.5)	7 (29.2)	2 (15.4)		
Charlson Comorbidity Index, mean (SD)	4.5 (1.6)	5 (1.4)	5 (1.6)	5.2 (1.2)	28.3	.246
Lines of treatment, median (IQR)	1 (1-2)	1 (1-2)	1 (1-2)	1 (1-2.5)	18.5	.422
Time since diagnosis in months, mean (SD)	34.5 (34.9)	40.8 (39.7)	44.1 (47)	35.5 (28.7)	8.9	.440
Currently on treatment, *N(%)*	38 (66.7)	64 (52.5)	15 (62.5)	6 (46.2)	4.3	.231
Type of current treatment, *N(%)*					10.8	.095
None	18 (31.6)	58 (47.5)	9 (37.5)	7 (53.8)		
Active therapy	24 (42.1)	33 (27)	12 (50)	2 (15.4)		
Maintenance therapy	14 (24.6)	29 (23.8)	3 (12.5)	4 (30.8)		
Intensity of received treatments, *N(%)*					**16.7**	**.054**
None	12 (21.1)	12 (9.8)	2 (8.3)	1 (7.7)		
Chemotherapy only	18 (31.6)	59 (48.4)	13 (54.2)	9 (69.2)		
Chemotherapy and stem cell transplant	26 (45.6)	49 (40.1)	9 (37.5)	3 (23.1)		

Regression analysis: predictors of poor and deteriorating quality of life

For determining which baseline characteristics predict a poor outcome in multiple myeloma patients, we first entered those variables found in univariate regression analysis to be significant into the multivariable model. The model was then trimmed to contain only those significant in multivariable analysis and adjusted for general symptom level (total number out of 15 symptoms experienced by each participant) (see Table 5). Experiencing a trajectory of poor or deteriorating QOL was predicted by baseline pain (*OR* = 1.2, 95% CI: 1.1-1.3, p = .042), presence of clinically relevant HADS anxiety (*OR* = 1.2, 95% CI: 1.0 – 1.4, p = .019) and HADS depression (*OR* = 1.2, 95% CI: 1.0 – 1.4, p = .040). Compared to the reference group of ECOG performance status 0 (Fully active), participants with poor or deteriorating QOL had lower odds of being in the ECOG performance status group 2 (ambulatory but unable to carry out work activities) (*OR* = 0.2, 95% CI: 0.1- 0.9, p = .042).

Table 5. Results of multivariable logistic regression models of predictors for joint poor QOL (class 3) and deteriorating QOL (class 4), n = 37

	B	S.E.	Wald	OR	95% Lower CI	95% Upper CI	p-value
Constant	-4.3	1.4	9.7	**0.013**	-	-	**.002**
ECOG 0 (reference)	-	-	6.9	-	-	-	.076
ECOG 1	-0.3	0.9	0.1	0.8	0.1	4.4	.752
ECOG 2	-1.7	0.8	4.2	**0.2**	**0.1**	**0.9**	**.042**
ECOG 3 and 4	-0.5	0.9	0.4	0.6	0.1	3.3	.551
General symptom level	0.3	0.2	4.5	**1.3**	**1.1**	**1.6**	**.035**
Fatigue	-0.1	0.1	0.4	0.9	0.9	1.0	.551
Pain	0.2	0.1	4.2	**1.2**	**1.1**	**1.3**	**.040**
Breathlessness	0.1	0.1	1.3	1.1	0.9	1.1	.256
Drowsiness	-0.4	0.5	0.9	0.7	0.3	1.6	.349
Anxiety	0.2	0.1	5.5	**1.2**	**1.0**	**1.4**	**.019**
Depression	0.1	0.1	4.2	**1.2**	**1.0**	**1.4**	**.040**

Discussion

This study is the first to describe and compare the longitudinal patterns of change in QOL and palliative care concerns in patients with multiple myeloma. We successfully investigated the heterogeneity in the course of HRQOL trajectories across an 8-months study period and determined four classes of trajectories. To capture the breadth of the QOL experience of MM patients, we did not restrict our sample to a specific group of patients on chemotherapy or newly diagnosed patients eligible for first-line treatment. Within all QOL trajectories, the two largest classes (class 1, 26.4%, and class 2, 56.5%) were characterised by improving and stable, good HRQOL. Notably, MM patients in class 1 showed a much lower intercept than patients in class 2, indicating that they experienced poor HRQOL at the beginning of the observation period and then substantially improved over the course of 8 months. The initial intercept of class 2 was much higher, suggesting that this group started with a better QOL and remained relatively stable in the next months. In comparison, patients in classes 3 (11.1%) and 4 (6%) experienced either a poor QOL throughout the 8 months observation period or, as in class 4, showed the most severe trajectory of deteriorating QOL. Class membership was not associated with stage of disease. Thus, experiencing a stable trajectory of QOL or a course of improving QOL was not associated with being in a stable, treatment-free interval or with recovering from first- or second-line treatment. Rather, members of trajectory classes 3 and 4 were those with higher general symptom levels, a higher pain level, a poor ECOG performance status (unable to carry out work activities), and with clinically relevant levels of anxiety and depression.

Strengths and limitations

Our observational study is based on a large, representative sample of patients with multiple myeloma that were sampled from different settings and at different stages of their disease. This lends greater representativeness to the findings than possible in treatment-defined samples [51] or clinical research samples that are usually composed of more carefully selected individuals and oversample younger patients with less comorbid disease [52]. The drawback of this methodology is that patients were consecutively enrolled in the participating centres, resulting in a convenience sample. The outpatient setting and possible gate-keeping from recruiting staff might have resulted in a higher proportion of patients with stable disease and a lower symptom burden having been included in this study. The group for which predictors were modelled, consisting of patients with poor or deteriorating QOL, was comparably small to the larger classes of improving and stable, good QOL. This will have reduced analytical power [46]. Latent class growth models for HRQOL only included baseline predictors. Time-varying covariates were not included in the model due to the comparably small sample size. Other covariates that were not included in the model may have influenced the HRQOL trajectories. In particular, information on response to treatment [22] and important biomedical variables such as albumin, C-reactive protein [52], haemoglobin levels [53], and possible cytokines [54,55] might have altered the number and odds ratios yielded in the logistic regression analysis. Future research needs to investigate the relationship between patient-reported outcomes like symptoms and QOL and these biomedical variables and their respective strength for indicating deteriorating disease and potential need for palliative care involvement. Findings of this study need to be validated in larger samples and specifically in a study with a longer follow-up period during which more patients progress through intervals of high-dose treatment and stable, treatment-free phases to see the evolution of QOL.

Comparison with other research

Longitudinal studies are rare in multiple myeloma. Most of the evidence on QOL is presented as secondary endpoint data in clinical trials or in longitudinal studies of patients receiving haematopoietic stem cell transplant populations [54-57]. Only one longitudinal observational study using a population perspective could be identified [10]. Mols et al. (2012) [10] assessed myeloma-specific QOL at two time points with the EORTC QLQ-C30 and its myeloma MY20 module. They described a generally poor QOL compared to an age- and gender-matched normative sample. Worsening of symptoms such as pain, peripheral neuropathy, drowsiness, but also psychosocial problems such as worries about the future and about dying, was observed. However, in this registry-based study only two measurement points, one year apart, were used to evaluate the mean trajectory of QOL. Studies of SCT populations [54-57], on the contrary, report

an increase in QOL over the course of the first two years after transplantation. Only depression and life satisfaction have been reported as persistent areas of concern [56].

In our study we observed a large heterogeneity in the QOL trajectories that was not captured in the mean change in QOL over time. Compared to the available longitudinal evidence, our findings highlight that within an average trajectory of stability or improvement, subgroups of patients exist whose QOL trajectories differ substantially from the overall course. The logistic regression analysis identified five variables, general symptom level, pain, anxiety, depression and ECOG performance status as significant predictors of poor or deteriorating QOL in MM. This result is similar to multivariable regression analyses in two recent, observational cross-sectional studies in myeloma [58,59]. Jordan and co-authors determined symptom burden in 154 MM patients [59]. Fatigue and bone pain were the most frequent symptoms and were strongly associated with global QOL, as were depression, general symptom level, disease duration and being currently on treatment. Also, a study of stable but advanced stage MM patients identified pain and fatigue as the most frequent symptoms, impacting negatively on physical functioning [58]. Similarly, these studies did not identify clinical factors such as comorbidities or type of treatment as significantly associated factors for QOL. The importance of physical functioning, symptoms and psychosocial distress and their higher predictive power compared to disease parameters have been demonstrated in three studies prognostic studies [26-28]. For example, psychosocial QOL scales were associated with overall survival, whereas none of the disease parameters (ISS stage, creatinine, LDH, M-protein level and albumin level) explained a substantial proportion in the overall variability of QOL parameters [27].

Policy implications and conclusions

Despite recent guidelines pleading the access of haematological cancer patients to palliative care services due to the high symptom burden in this group [10,11], these patients, particularly more chronic haematological malignancies such as multiple myeloma, miss out on SPC [19-21]. Reasons are the unpredictability of the disease trajectory with the potential for sudden deterioration and death as well as attitudinal barriers resulting from equating palliative care with end of life care [17,18]. Our findings demonstrate that in order to reach haematological cancer patients early enough during times of high palliative care needs, the model of care needs to change. The result of a subgroup of patients consistently experiencing poor or deteriorating QOL calls for early identification of these patients and early integration of palliative care alongside anti-myeloma treatment regimens [16]. In particular, possible targets that indicate suitability for palliative care involvement are patients that experience a high general symptom level, high levels of psychosocial distress, pain and low physical functioning. In order to identify these patients in clinical practice, routine monitoring of symptoms and QOL is warranted.

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Author contribution

CR detailed methods for the study, led the application for ethical approvals, collected the data, planned and conducted the data analysis and drafted the manuscript, supervised by IJH, GW and RJS. IJH led the application for funding for this programme of work, which included this study, in collaboration with SAS, RJS and PME, and acted as senior researcher overseeing the project and publications. All authors contributed to the preparation of the manuscript and read and approved the final manuscript.

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Supplementary material

Figure S1. The Myeloma Patient Outcome Scale

For staff use
Patient number:

My-POS Patient Version

www.pos-pal.org

Name:.....

Date (dd/mm/yyyy): ____ / ____ / ____

Please answer the following questions by ticking the box that is most true for you. It is important to answer all of the questions if possible. Your answers will be used to help improve your care and the care of others.

Thank you.

Q1. What are your main problems or concerns at the moment?

1. .....
2. .....
3. .....

Q2. Below is a list of symptoms, which you may or may not have experienced. For each symptom please tick one box that best describes how it has affected you over the past week.

	No, not at all	*Slightly*	*Moderately*	*Severely*	*Overwhelmingly*
Pain	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐
Shortness of breath	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐
Weakness or lack of energy	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐
Nausea (feeling like you are going to be sick)	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐
Vomiting (being sick)	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐
Poor appetite	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐
Constipation	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐
Sore or dry mouth	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐
Drowsiness	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐
Poor mobility	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐
Diarrhoea	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐
Tingling in the hands and / or feet	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐
Difficulty remembering things	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐

Please list any other symptoms not mentioned above, and tick one box to show how they have affected you over the past week.

1. _____ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐
2. _____ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐
3. _____ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐

MyPOS Patient Version 4

		No, not at all	*Occasionally*	*Sometimes*	*Most of the time*	*Yes, always*
Q3.	**Over the past week, have you been feeling anxious or worried about your illness or treatment?**	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐
Q4.	**Over the past week, have any of your family or friends been anxious or worried about you?**	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐
Q5.	**Over the past week, have you been feeling depressed?**	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐

		Yes, always	*Most of the time*	*Sometimes*	*Occasionally*	*No, not at all*
Q6.	**Over the past week, have you felt at peace?**	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐

		Yes, as much as I wanted	*Most of the time*	*Sometimes*	*Occasionally*	*No, not at all*
Q7.	**Over the past week, have you been able to share how you are feeling with your family or friends?**	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐

		Enough information the right amount for me	*Information received but hard to understand*	*Information received but would like more*	*Very little information and would like more*	*No information received and would like information*
Q8.	**Over the past week, have you had as much information as you wanted?**	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐

		No problems / Problems addressed	*Problems being addressed*	*Problems partly addressed*	*Most problems not addressed*	*Problems not addressed at all*
Q9.	**Over the past week, have any practical matters resulting from your illness been addressed? (such as financial or personal)**	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐

Please turn to the next page.

MyPOS Patient Version 4

Figure S2. Study flow chart

Number screened	524	Ineligible	120	
		Feeling too unwell		36
		No english		26
		No capacity		5
		No confirmed diagnosis		38
		Myeloma not main problem		15
Number approached	404	Not recruited	154	
		Not interested in study		73
		Feeling too unwell		8
		Too short of time		25
		Participating in other study		21
		No reasons given		27
Number recruited	250	Not returned questionnaire	12	
		No longer interested in study		0
		Feeling too unwell		3
		Died		1
		No reason given		8
Completed first questionnaire	238			
Completed second questionnaire	199	Lost in post		2
	(83.6%)	feeling too unwell		6
		died		2
		too burdensome		3
		no reasons given		26
Completed third questionnaire	171	Lost in post		5
	(71.8%)	feeling too unwell		3
		died		2
		moved		1
		no reasons given		19
Completed fourth questionnaire	150	Lost in post		5
	(63.0%)	feeling too unwell		5
		died		4
		moved		1
		no reasons given		12
completed fifth questionnaire	125	died		1
	(52.5%)	no reasons given		31

Table S3. Fit indices for the general growth mixture models of the baseline value and probability of class membership

#	Log likelihood	Par	BIC	aBIC	AIC	Entropy	BLRT p-value	Group sizes (n)
2	-2744.59	13	5559	5517	5515	.750	.000	52/164
3	-2733.55	16	5553	5502	5499	**.764**	.000	52/153/11
4	-2724.23	19	**5550**	5490	5486	**.758**	.013	13/122/57/24
5	-2716.26	22	**5550**	**5481**	**5476**	.756	.000	56/115/22/13/10
6	-2711.73	25	5557	**5478**	**5473**	.734	.098	29/30/11/18/115/13

Note: Best fit indicators are in bold.
Abbreviations: LogL Log-Likelihood statistic, Par: Number of free model parameters, BIC: Bayesian Information Criterion, ABIC: sample-size adjusted Bayesian information criterion, AIC: Akaike information criterion, BLRT: boot-strapped likelihood ratio test, MyPOS: Myeloma Patient Outcome Scale

Table S4. Results of sensitivity analyses: complete case versus weighted imputation and multiple imputation

	Complete case		Weighted imputation		Multiple imputation	
	OR	p	OR	p	OR	p
Constant	**0.013**	**.002**	**0.055**	**.003**	**0.055**	**.003**
ECOG 0 (reference)	-	.076	-	.445	-	.078
ECOG 1	0.8	.752	1.8	.451	0.8	.753
ECOG 2	**0.2**	**.042**	**0.3**	**.025**	**0.2**	**.040**
ECOG 3 and 4	0.6	.551	1.3	.766	0.6	.620
General symptom level	**1.3**	**.035**	**1.4**	**.049**	**1.4**	**.024**
Fatigue	0.9	.551	**1.01**	**.048**	1.0	.552
Pain	**1.2**	**.040**	**1.1**	**.045**	1.2	.039
Breathlessness	1.1	.256	1.0	.389	1.1	.256
Drowsiness	0.7	.349	1.0	.826	0.7	.349
Anxiety	**1.2**	**.019**	**1.2**	**.037**	**1.2**	**.037**
Depression	**1.2**	**.040**	**1.2**	**.038**	**1.2**	**.038**

7 Results: Longitudinal validity and reliability of the Myeloma Patient Outcome Scale (MyPOS)

In this chapter, I present the last empirical part of this PhD study, the longitudinal psychometric analysis of the MyPOS with specific focus on its item quality for longitudinal individual monitoring, its responsiveness to change and its test-retest reliability. The objectives of this part were:

a) To evaluate the validity and item quality of the MyPOS and its scale in myeloma patients at different stages in their disease trajectory,

(b) to determine the reliability of the MyPOS over time (test-retest reliability) within a Generalizability framework,

(c) to determine the responsiveness and clinical significance of changes in quality of life scores and subscale scores and estimate the minimal important change (MID), both for patients who deteriorated and improved, and

(d) to explore the acceptability of frequent self-monitoring of HRQOL.

The article presented was submitted to *Quality of Life Research* in April 2016. The main article text formatted in the style of the journal is presented, followed by supplementary material that was submitted to the journal as an online appendix.

Title: Longitudinal validity and reliability of the Myeloma Patient Outcome scale (MyPOS) was established using traditional, generalizability and Rasch psychometric methods

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Abstract

Purpose. The Myeloma Patient Outcome Scale (MyPOS) was developed to measure quality of life in routine clinical care. The aim of this study was to determine its longitudinal validity, reliability, responsiveness to change and its acceptability.

Methods. This 14-centre study recruited patients with multiple myeloma. At baseline and then every two months for 5 assessments, patients completed the MyPOS. Psychometric properties evaluated were: (a) confirmatory factor analysis and scaling assumptions, (b) reliability: Generalizability theory and Rasch analysis, (c) responsiveness and minimally important difference (MID) relating changes in scores between baseline and subsequent assessments to an external criterion, (d) determining the acceptability of self-monitoring.

Results. 238 patients with multiple myeloma were recruited. Confirmatory factor analysis found three subscales, criteria for scaling assumptions were satisfied except for gastrointestinal items and the *Healthcare support* scale. Rasch analysis identified limitations of suboptimal scale-to-sample targeting, resulting in floor effects. Reliability indices were good for monitoring quality of life over time (R = 0.42 to 0.98). Responsiveness analysis yielded an MID of +2.5 for improvement and -4.5 for deterioration.

Conclusions. The MyPOS demonstrated good longitudinal measurement properties. It can be used in routine clinical care to monitor symptoms and changes in health-related quality of life and therefore guide patient care. The new psychometric approaches should be used for testing validity of monitoring in clinical settings.

Introduction

Cancer is a major public health concern, being the second leading cause of death worldwide [1]. With the aging of the society, cancer incidence is rising [2,3]. Despite advances in treatments, many cancer patients still face long disease trajectories and incurable disease. Multiple myeloma, an incurable cancer of the bone marrow and the second most common haematological malignancy [4], exemplifies this changing face of cancer. Many myeloma patients experience a more chronic disease trajectory, coping with gradually progressing disease, interspersed with intervals of stable disease with minimal or maintenance treatment but lasting effects of high-dose chemotherapy [5,6]. This longer disease trajectory of cancer and the intensive treatments have led to a need to evaluate patient-reported outcomes in addition to traditional monitoring, such as response to treatment and toxicity profiles, in this condition.

Patient-reported outcomes primarily comprise symptoms and health-related quality of life (HRQOL). Incorporating longitudinal assessment into routine clinical practice has shown benefits such as better symptom control, improved patient-clinician communication and satisfaction with care [7,8]. In trials, serial assessment of HRQOL incorporates the patient's experience while monitoring treatment safety and efficacy [9]. It also aids prognosis in chronic conditions and in haematological malignancy [10-12].

Despite these benefits, few measures are designed for monitoring HRQOL in routine clinical settings [13,14]. A systematic review of 13 generic and disease-specific HRQOL measures in multiple myeloma [13], found no single tool developed or validated for this purpose. Consequently, the Myeloma Patient Outcome Scale (MyPOS), a questionnaire to measure disease-specific HRQOL and palliative care concerns, was developed and validated in a cross-sectional sample of 380 community and inpatient myeloma patients in the United Kingdom (UK) [15]. However, the clinical utility of the MyPOS in form of longitudinal validity and reliability [16-19] still needs to be established.

The psychometric criteria for longitudinal monitoring validity are still ill-defined. Traditional psychometrics and associated guidelines focus on usages of assessment or screening [20-22]. The notable exception is McHorney's study of individual patient-monitoring in which the following criteria were proposed [23]: (i) practical features (brief measures, easy administration, easy score interpretation), (ii) breadth of health measured (variety of health concepts with assessing the full range of health from disability to well-being), (iii) depth of health measured (minimal floor and ceiling effects), (iv) precision for cross-sectional assessment (precise reliability estimates, e.g. Cronbach's alpha, with small standard error of measurement) (v) precision for longitudinal monitoring (high reproducibility/test-retest reliability with small standard error of measurement), and (vi) validity (satisfactory convergent/divergent validity, high responsiveness/sensitivity to

clinical change and definition of individual patient application, e.g. screening, monitoring, decision-making, tested). The authors also recommend more stringent benchmarks for measurement errors to fit the longitudinal use of measures [23]. Building on this work, we propose to extend McHorney *et al*'s framework by incorporating new psychometric approaches, particularly Rasch analysis [24,25] and Generalizability theory [26-28], to further test some of their six quality criteria for longitudinal monitoring applications. Particularly Generalizability theory has been used successfully in psychological studies that monitored emotional changes [46]. Both techniques are suitable since they address the limitations of classical test theory (CTT) by providing individual item information, information on item invariance and person-level indicators that help understand floor and ceiling effects, understanding sources of measurement error, and the ability for discriminating among different patient groups (i.e. disease severity) [24,25,28,29]. In particular, we propose to extend analysis for criteria (iii), depth of health measured, (iv) precision for cross-sectional assessment, and (v) precision for longitudinal monitoring by using person-item targeting in Rasch analysis to further understand floor and ceiling effects (iii), and to use the variance decomposition method for forming reliability indices beyond simple test-retest reliability, to understand how reliable the use of an instrument is in the situation of screening HRQOL at one point in time, monitoring HRQOL over time and detecting change over time (iv and v, [46]).

We aim to examine the longitudinal validity and reliability of the MyPOS. The objectives were: (a) to evaluate the validity of the MyPOS and its scale in myeloma patients at different stages in their disease trajectory, (b) to determine the reliability of the MyPOS over time (test-retest reliability) within a Generalizability framework, (c) to determine the responsiveness and clinical significance of changes in quality of life scores and subscale scores and estimate the minimal important change (MID), both for patients who deteriorated and improved, and (d) to explore the acceptability of frequent self-monitoring of HRQOL.

Methods

Study design and participants

This multi-centre, prospective longitudinal study recruited patients with multiple myeloma at different disease stages. Patients were enrolled in the study from March 2014 until July 2015. Inclusion criteria were: older than 18 years, confirmed diagnosis of multiple myeloma that had been disclosed to the patient, and capacity to give informed written consent. Patients who were too unwell, distressed or symptomatic to participate, as judged by their clinical team, were excluded, as were patients with severe neutropenia or for whom myeloma was not the most important health problem. Patients were recruited from 14 hospital trusts in the United Kingdom, both from secondary and tertiary centres. Study procedures followed the guidelines of the

Helsinki Declaration. Ethical and research governance approvals were obtained from the Central London Ethics Committee (13/LO/1140) with further local Research and Development approvals from all participating National Health Service (NHS) hospital trusts.

Procedures

Consenting patients were invited to complete questionnaires at baseline and then every two months for a total of five assessments and a maximum follow-up time of 8 months post-baseline. The first questionnaire was given to patients when they attended outpatient clinics. Subsequent questionnaires were sent via mail, with a self-addressed, pre-stamped envelope provided for return, a pen and a sweet to boost participation [30]. Patients were followed, if possible, if they moved to a nursing home, hospital, or hospice. We sought information about any deaths that occurred.

Questionnaires

Participants completed the Myeloma Patient Outcome Scale [15]. The MyPOS is a module of the Palliative Care Outcome Scale (POS) [31-33], extended by myeloma-specific concerns. It comprises a list of 13 symptoms and 20 quality of life or palliative care concerns items. Items are scored on a 5-point Likert scale ranging from 0 ‘not at all’ to 4 ‘overwhelmingly’ and summed to form a total score (total possible score: 132). A higher total MyPOS score indicates more problems. Content and construct validity of the MyPOS have been established in a clinically representative sample [15,34].

To evaluate the responsiveness and minimal important change on the MyPOS, an independent question to assess the degree of change was used. This global rating of change question (GRC) [22,36] asked ‘Has your overall quality of life changed since the first time you completed this questionnaire?’, with patients indicating whether their quality of life had got worse, stayed the same, or had improved. The GRC question was part of each follow-up assessment.

The questionnaire sent at the third assessment contained three open-ended questions to explore the acceptability of frequent self-monitoring. The questions concerned the suitability of the MyPOS for monitoring quality of life, the potential usefulness of monitoring quality of life and how results could be used by patients and clinicians.

Statistical analysis

Table 1 provides an overview of analyses methods per objective, following the McHorney *et al* framework [23], and details the criteria that were used for establishing fit and validity/reliability. All quantitative data analyses were conducted in SPSS v.22 [52], lavaan package in R [53] and

partial credit Rasch models were run in RUMM2030 [54]. Patients with three or more missing MyPOS questionnaires at the follow-up time points were excluded from statistical analyses. If more than 50% of responses within a scale were missing from one questionnaire, it was removed from the analysis. Missing data in the confirmatory factor analysis were imputed using a multiple imputation approach [37]. Responsiveness analyses and Rasch analysis used a complete case analysis without imputation of missing data.

For construct validity (*objective 1*), re-evaluating the subscale structure defined in the initial validation [15] was necessary due to the sample-dependency of CTT approaches [55]. Confirmatory factor analyses contrasting three models to find best fit of the data were used: (i) a unidimensional model (one factor) solution, (ii) three factor solution replicating the solution from the initial validation [15] with symptom and functioning items loading on one factor, separate from factors emotional response and healthcare support, and (iii) an adapted three-factor solution with all functioning items loading onto the emotional response factor, resulting in three subscales Symptoms, Functioning and Emotional response, and Healthcare support. Scaling assumptions of the total MyPOS score, subscale scores and individual item scores were evaluated using Rasch analysis. A partial credit Rasch model was fitted to each subscale, *Symptoms* (13 items), *Emotions* (17 items) and *Healthcare Support* (3 items), separately. Floor/ceiling effects and distribution of item responses were checked using descriptive statistics and Rasch analysis (person-location maps). Presence of floor or ceiling effects is indicated in the person-location map by mean item location scores not matching the whole range of person locations at the lower or upper end of the scale [57]. This indicates either items missing from the measure to represent very good or poor HRQOL, or indicates that the sample used for evaluation of the measure is not well-targeted to comprise all levels of severity that the MyPOS measures [44]. For establishing the test-retest reliability and invariance of the MyPOS (*objective 2*) for participants that indicated they did not experience a change in their condition over time, the Generalizability theory framework was used [26-28]. Four generalizability coefficients [46] were computed (see Table 1). Item invariance was further tested using Rasch analysis following Hobart *et al's* [55] approach using differential item functioning (DIF). DIF is an indicator of items not performing in a stable/invariant way since the expected values on the item are not the same for all subgroups in the sample (i.e. groups of different disease severity or functional ability) [55]. *Objective 3*, establishing the responsiveness to change and the minimal important difference for the MyPOS, followed guidelines by Guyatt [50] and used a combination of anchor-based, distribution-based approaches. For responsiveness, we used the GRC to identify patients that experienced change over time, with categories improved, unchanged and deteriorated to examine the differences in mean score changes between each time point and baseline (T2 to T1, T3 to T1, T4 to T1, T5 to T1). We determined ROC curves separately for improvement and deterioration (improved vs. stable or deteriorated vs.

stable) for total MyPOS score and the three subscale scores. For *objective 4* we analysed participant's written comments in the open-ended questions of the MyPOS using thematic analysis [51].

Table 1 Overview of measurement properties and criteria for assessing longitudinal validity and reliability

Measurement property	Statistical methods
Objective 1: Further validity of the MyPOS	
Maximum-likelihood confirmatory factor analysis [37]	Goodness-of-fit indices: a) $Chi^2/df > 2$ [38] b) Comparative fit index (CFI) of ≥ 0.90 [39] c) Root mean square error of approximation (RMSEA) of ≤ 0.60, 90% confidence interval 0.05 to 0.08 [39] d) Non-normal fit index (NNFI) of ≥0.95 or normal fit index (NFI) of ≥0.95 [39] Checks of unidimensionality for Rasch scaling via principal component analysis and independent t-tests [40,41]: a) RMSEA <0.08 [42] b) CFI >0.90 [43] c) Tucker-Lewis Index (TLI)>0.90 [39]
Floor and ceiling effects via descriptive and Rasch analysis	• Data completeness and distribution of item responses • >10% missing from lower or upper end of the scale [16] • Rasch analysis: Scale-to-person targeting, the ability of the scale to cover the whole range of person estimates, shown on the person-item threshold distribution map [44]
Scaling assumptions via Rasch analysis: • Fit to the Rasch model • Fit of individual items • Person fit • Reliability • Response options • Redundant items	• *Fit to the Rasch model*: Non-significant X^2-test [44] and RMSEA <0.2 [39]. However, large sample size can inflate the X^2 value and increase the likelihood of identifying misfit [39]. • *Individual item fit*: Fit residual range -2.5 to +2.5 [44]. The residuals indicate the level of agreement between the observed and expected responses with perfect fit being given if a mean residual is zero with a standard deviation falling between -1 and +1. Positive fit indices above +2.5 show misfit to the model, negative fit indices below -2.5 indicate redundancy of items. Item characteristic curves were examined for graphical item fit. • *Person fit*: Same criteria as item fit. • *Reliability*: Person Separation Index (measure of internal consistency in Rasch analysis) ≥ 0.70 [45] • *Response options:* Category probability curve maps for each item examined for disordered answer options, signifying ambiguous labelling or abundance of response options. • *Redundant items*: Residual correlation matrix, identifying pairs of items with high correlation coefficients (≥0.3) [44]
Objective 2: Test-retest reliability/item invariance of the MyPOS	
Test-retest reliability using Generalizability theory	Restricted maximum-likelihood variance decomposition (VARCOMP) with participants and interaction terms as random factors and items and days as fixed factors. The variance associated with each component of variation, systematic between-person differences in mean item levels, true within-person change over time, idiosyncratic item responses and random measurement error, is partitioned [27,28]. These variance estimates are used to form indices of the reliability for discriminating between-persons (between-person differences) and within-person change. Four generalizability coefficients (all >0.5 [46]): • R_{IF}: Reliability of assessment/screening (*Is the MyPOS reliable at each assessment?)*

	• R_{IR}: Reliability of discrimination (*Can the MyPOS reliably distinguish between persons over time?)* • R_{KF}: Test-retest reliability (*Is the MyPOS reliable over time?)* • R_c: Within-person reliability of change (*Can the MyPOS assess change in one person over time?)* It should be noted that determination of test-retest reliability within Generalizability theory is a model-based approach that derives reliability indices from variance decomposition as an alternative way to intra-class correlation coefficients. Analysis of test-retest reliability was based on the subgroup of stable patients as indicated by the global rating of change ("unchanged" – see Objective 3, Responsiveness).
Item invariance using Rasch analysis	Differential item functioning (DIF) via a two-way ANOVA of standardised residuals with Bonferroni correction for type I error [47]; assessing whether item mean scores showed significant change over all five assessments [44] • Significant interaction between class interval (level of quality of life) and time indicates a non-uniform DIF and an unstable, unreliable item.
Objective 3: Responsiveness and minimal important difference (MID(for MyPOS	
Responsiveness	GRC to categorise patients into: (a) improved overall QOL (b) deteriorated overall QOL (c) unchanged Differences in mean score changes between each time point and baseline were assessed and graphed. The adequacy of the anchor was assessed via Spearman correlation [17].
MID: Anchor-based approach	• Receiver-operating characteristic curve (ROC) to determine optimal cut-off points separately for improvement and deterioration, according to GRC ratings [48]. • MID: cut-off point on ROC for which the sum of percentages of false-positive and false-negative classifications [(1-sensitivity or true positive rate) + (1-specificity or false positive rate)] is smallest [36]. • Significance of the area under the curve with a p-value >0.5 indicates changes on the MyPOS scores are associated with the gold standard GRC criterion [36]. • Graph of distribution of change scores, MIDs and 95% CIs [49].
MID: Distribution-based approach	• Standard deviation at baseline used to estimate MID [50] • Following Cohen's criteria [84], small changes (0.2 x SD), moderate changes (0.5 x SD) and large changes (0.8 x SD) were computed. A moderate effect size change was designated as the MID [50].
Objective 4: Acceptability of monitoring	
Acceptability	Thematic analysis of responses to open-ended questions about views on self-monitoring and data feedback were analysed using thematic analysis [51].

Results

Characteristics of patients and questionnaire completion

250 patients were recruited of whom 238 completed the questionnaire at baseline. Mean age was 68.5 (range: 34-92 years), mean time post diagnosis was 3.3 years with 139 (25.5%) patients who had been living with myeloma 5 years and longer (see Table 2). 199 participants completed time point 2 (83.6%), 171 completed time point 3 (71.8%), 150 completed time point 4 (63%) and 125 (52.5%) completed the last time point 5 questionnaire. Of the 113 patients lost to follow-up, 9 had died, 17 had been feeling too unwell to continue with the study, 2 had moved, and 86 gave no reason for discontinuing the study. 12 questionnaires were lost in the mail.

At baseline, 3.3% of responses in returned questionnaires were missing. The number of missing responses reduced over time: 1.2% at time point 2, 0.7% at time point 3, 0.7% at time point 4 and 0.9% at last follow-up time point.

Table 2 Demographic and clinical characteristics of 238 patients with myeloma included in the study

Variable	
Age, *Mean ± SD (range)*	68.5 ± 10.5 (range 34-92)
Men, *N(%)*	147 (61.8)
Married, *N(%)*	170 (71.4%)
White background, *N(%)*	220 (92.4%)
Education level, *N(%)*	
Secondary school	137 (57.5)
Technical qualification	52 (21.8)
University	41 (17.3)
Working, *N(%)*	41 (17.2%)
Type of myeloma, *N(%)*	
IgA or IgG	180 (78.6%)
Light chain disease	39 (16.4%)
Other	9 (3.8)
ISS stage at diagnosis, *N(%)*	
I	68 (28.6%)
II	41 (17.2%)
III	52 (18.6)
Time since diagnosis (in months), *mean (SD)*	39.1 (38.2)
Disease stage, *N(%)*	
Newly diagnosed	38 (15.9)
Stable/plateau	128 (53.8)
Relapsed/progressive/refractory disease	72 (30.3)
Currently receiving treatment, *N(%)*	118 (49.6)
Active therapy	80 (33.6)
Maintenance therapy	38 (15.9)
Intensity of treatments received, *N(%)*	
Chemotherapy only	111 (46.7)
Chemotherapy and HSCT	76 (31.9)
Two or more HSCT	15 (6.3)
Lines of treatment received, *mean (SD)*	1.5 (1.2)
ECOG performance status, *N(%)*	
0 Fully active	79 (33.2)
1 Restricted	104 (43.7)
2 Unable to work	33 (13.9)
3 or 4 – Limited self-care/bed-bound	15 (6.3)
Charlson comorbidity index, *mean (SD)*	4.9 (1.5)
General symptom level (MyPOS), *N(%)*	
0	3 (1.3%)
1 – 5	70 (29.4%)
6 – 8	65 (72.3%)
9 – 15	92 (38.7%)
Mean number of symptoms, *Mean ± SD*	7.4 ± 3.6
Total MyPOS, *Mean ± SD*	26.0 ± 16.8

Note: Initial induction and HSCT were counted as one single line of treatment. Likewise, if during a line of treatment the anti-myeloma therapy was changed due to unresponsiveness or side effects, this was still counted as one line. If active treatment was followed by maintenance treatment, active and maintenance were counted as one line. A treatment-free interval was defined by not receiving active or maintenance anti-

myeloma therapy, whereas supportive therapies (e.g. bisphosphonates or anti-anaemia treatment) were possible.
Abbreviations: ECOG, Eastern Cooperative Oncology Group performance status; HSCT: haematopoietic stem cell transplantation; IgA, immunoglobulin A; IgG: immunoglobulin G; ISS: International staging system for multiple myeloma; MyPOS, Myeloma Patient Outcome Scale; SD, standard deviation.

Confirmatory factor analysis of the MyPOS and Rasch scaling

Confirmatory factor analysis

Factor analysis confirmed a three-factor structure but with functioning items now loading onto the Emotional response factor (solution iii). The fit indices indicated a satisfactory model fit. Although the X^2 test was significant, the RMSEA (0,056; 90% CI 0.050 – 0.063) and the CFI (0.942) were satisfactory. When compared to the uni-dimensional solution, the three-factor solution performed best. The three factors together explain a total of 42.2% of the variance with the three subscales explaining 28.1, 7.2, and 6.9%, respectively. All items loaded above 0.40 on their respective subscales, except item 12 ("Tingling in the hands/feet, 0.378) and item 29 ("Worry about sex life", 0.189) (see Supplemental Table 1).

Rasch analysis

Overall fit of the data to the Rasch model for each subscale was given (see Supplemental Table 2). The range of item locations and item thresholds logits for all three subscales indicated that items mapped out a measurement continuum. The Symptom subscale had the widest range of item locations from -1.16 to +1.92 logits. The Healthcare support subscale had a range of item thresholds from a maximum of -3.07 to +5.28 logits. Regarding individual item fit, item 12 'Tingling in hands/feet' was the only item showing misfit in the Symptoms subscale with a fit residual of +2.68. In the Emotional response subscale, three items ('Sharing feelings with family/friends', 'Worry about sex life', 'Information about the future') showed misfit to the Rasch model (fit indices ranged from +2.52 to +3.16). All items in the Healthcare support subscale fitted the Rasch model (see Table 3). Examination of graphical fit via item characteristic curves confirmed good fit to the Rasch model for 30/33 items, except for 'Tingling in the hands/feet', 'Worry about sex life' and 'Information about future' (see Supplemental Figure 1). These show a slight under-discrimination, indicating difficulties to stratify participants according to different levels on the latent variable HRQOL.

Table 3 Myeloma Patient Outcome Scale item fit statistics ordered by location (n=238)

Item	Label	Threshold ordering	Item location	Standard error	Item fit residual	X^2	p-value	Threshold after collapsing response categories	Item fit residual after reordering	p-value after reordering
Subscale Symptoms										
1	Pain	✓	-0.48	0.08	-0.01	1.5	0.674	-	-	-
2	Breathlessness	✓	-0.44	0.09	0.65	4.6	0.201	-	-	-
3	Fatigue	✓	-1.16	0.09	-1.28	7.2	0.067	-	-	-
4	Nausea	x	0.46	0.11	-0.49	3.7	0.294	0 / 1(A little + Moderate) / 2(Severe + Overwhelming)	-0.82	0.209
5	Vomiting	x	1.92	0.15	-1.07	4.6	0.202	0 / 1 / 2	-1.76	0.028
6	Poor appetite	x	1.52	0.09	-1.34	3.2	0.357	0 / 1 / 2	-1.41	0.159
7	Constipation	x	-0.37	0.08	-0.43	2.5	0.472	0 / 1 / 2	-0.61	0.421
8	Sore or dry mouth	✓	-0.17	0.09	1.07	4.3	0.229	-	-	-
9	Drowsiness	✓	-0.27	0.09	-1.13	3.7	0.290	-	-	-
10	Poor mobility	✓	-0.59	0.08	-1.13	6.5	0.091	-	-	-
11	Diarrhoea	x	0.22	0.10	0.89	5.5	0.138	0 / 1 / 2	0.71	0.367
12	Tingling in hands/feet	✓	-0.41	0.08	**2.68**	16.7	**0.001**	0 / 1 / 2	2.39	0.011
13	Difficulty remembering	x	-0.21	0.09	0.25	1.5	0.687	0 / 1 / 2	0.64	0.339
Subscale Emotional Response										
14	Anxiety	✓	0.06	0.08	-2.18	15.3	**0.002**	0 / 1 / 2	-1.80	0.006
15	Family anxiety	✓	-0.26	0.07	0.87	0.7	0.864	0 / 1 / 2	0.53	0.974
16	Depression	x	0.29	0.08	-0.83	7.9	0.047	0 / 1 / 2	-1.32	0.035
17	At peace	x	-0.69	0.08	-1.69	13.9	**0.003**	0 / 1 / 2	-1.20	0.036
18	Sharing feelings	x	-0.03	0.07	**2.52**	3.6	0.308	0 / 1 / 2	2.49	0.041
19	Information	x	0.23	0.07	-0.13	2.6	0.453	0 / 1 / 2	-1.03	0.519
20	Practical matters	x	0.31	0.08	0.45	1.3	0.741	0 / 1 / 2	0.88	0.624
21	Usual activities	x	-0.26	0.07	0.21	1.7	0.639	0 / 1 / 2	-0.21	0.705
22	Hobbies	x	-0.66	0.06	0.81	8.5	**0.037**	0 / 1 / 2	-0.55	0.423
23	Quality time with family / friends	✓	0.26	0.08	-0.91	5.7	0.126	0 / 1 / 2	-1.06	0.301
24	Worry about sex	x	0.17	0.08	**3.16**	27.6	**0.001**	0 / 1 / 2	**2.79**	**0.001**

25	Worry about infections	x	0.15	0.08	1.45	4.3	0.228	0 / 1 / 2	1.22	0.223
26	Worry about physical appearance	✓	0.29	0.08	-0.17	0.3	0.953	0 / 1 / 2	0.13	0.402
27	Worry about financial situation	x	0.17	0.07	-0.02	3.0	0.391	0 / 1 / 2	0.44	0.285
28	Worry about illness worsening	✓	-0.50	0.07	-1.64	8.4	**0.038**	0 / 1 / 2	-1.72	0.010
29	Coping with illness and treatment	x	0.41	0.09	-1.93	19.3	**0.001**	0 / 1 / 2	-2.40	0.018
33	Information about future	x	0.06	0.07	**2.99**	19.4	**0.001**	0 / 1 / 2	**2.79**	0.044
Subscale: Healthcare Support										
30	Contact for advice	x	-0.69	0.15	0.46	1.8	0.411	0 / 1 / 2 / 3 + 4	1.27	0.109
31	Knowledge/skill of doctors	x	-0.14	0.17	0.25	5.3	0.069	0 / 1 / 2 / 3 + 4	0.56	0.023
32	Care and respect	x	0.83	0.24	-0.20	4.8	0.092	0 / 1 / 2 / 3 + 4	0.05	0.154

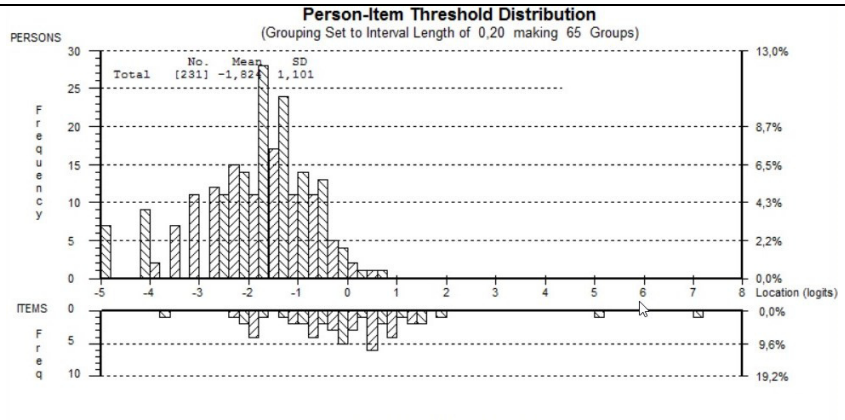
Note: Bolded values indicate fit residuals outside the recommended range of **-2.5** to **+2.5** or significant X^2-values.

Regarding item response options, thresholds were ordered for 12/33 items, but for 21/33 items the 5-point scale did not work in a linear way (see Supplemental Table 2). For ten of these items, people appeared to have difficulty discriminating between the last two to three categories, thus distinguishing a moderate problem from a severe or overwhelming one. For 11 items, people seemed to have difficulty discriminating between the first two categories ('not at all' and 'slight'/'moderate'). Fit for all items improved after removing extreme persons and rescaling the MyPOS items showing misfit and disordered thresholds to a 3-point Likert scale by combining categories "A little" and "Moderate", and combining "Severe" and "Overwhelming", the two highest response categories. After rescoring, all items on the Symptom subscale showed ordered thresholds. In the emotional subscale, item 19 (Having enough information about the illness") and item 33 ("Having enough information about what might happen in the future") retained disordered thresholds, as did item 32 ("Doctors/nurses show care & respect") on the Support subscale. Chi-square test statistics and the person separation index did not improve on this last subscale after rescoring and the Support subscale does not fit the Rasch model.

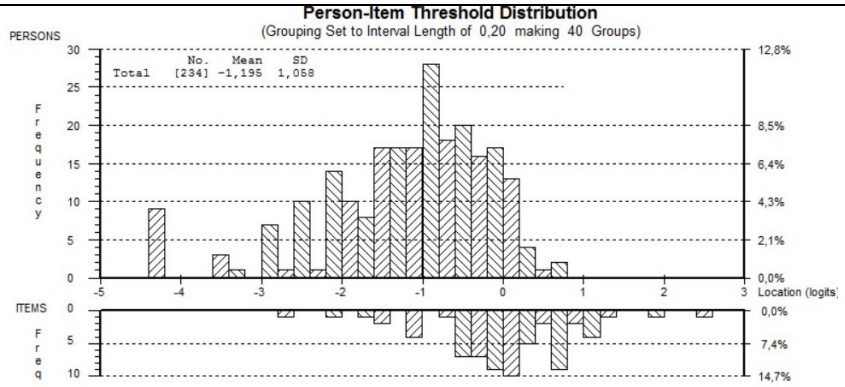
Some item redundancy was present for seven pairs of items that had residual correlations exceeding $r<0.30$ (3% of total correlations). The following item pairs showed potential redundancy: Nausea-Vomiting ($r = +0.37$), Feeling at peace-Depression ($r = +0.36$), Sharing feelings with family-Family anxiety ($r = -0.39$), Hobbies-Usual activities ($r = +0.36$), Worry about illness worsening-Anxiety ($r = +0.35$). Two pairs of items in the Healthcare support subscale correlated highly: Contacting doctors for advice – Knowledge of staff ($r = -0.82$) and Contacting doctors for advice-Doctors showing respect ($r = -0.55$).

Figure 1 Targeting of the sample (person-item location distribution maps) for the three subscales Symptoms (first panel), Emotional response (second panel), and Healthcare Support (third panel)

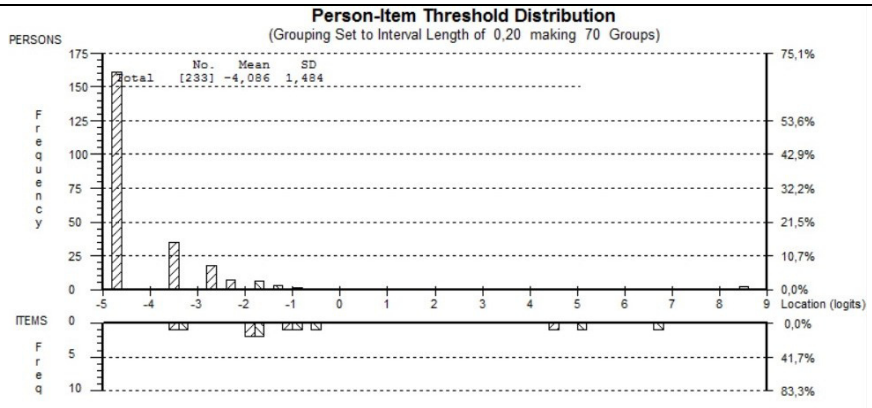
Subscale Symptoms (13 items)



Subscale Emotional response (17 items)



Subscale Healthcare support (3 items)



Note: The figure shows the distribution of person measurements (upper histogram) against the distribution of item locations (lower histogram). People are located along a continuum of low quality of life (left-hand side) to better quality of life (right-hand side). Items are located relative to their difficulty: easier items (representing lesser impact on quality of life) on the right-hand side, and the most difficult items (required

for a better quality of life) on the left-hand side. People outside the scales measurement range (-2 to +2 logits) indicate suboptimal scale-to-scale targeting. A ceiling effect is seen when the person locations on the left-hand side do not cover the item locations below, meaning items not discriminating in the portion of the sample with high quality of life.

Floor and ceiling effects

For most items, all response options were endorsed. However, 10/33 items ('Nausea', 'Vomiting', 'Poor appetite', 'Sore or dry mouth', 'Diarrhoea', 'Drowsiness', 'Tingling in the hands/feet', and three items in the Healthcare support subscale) had floor effects with participants not using the two highest levels. These were also the items with the most skew. Up to 18/33 items had percentages of >50% of participants choosing the option 'Not at all'. The MyPOS total score and subscale scores showed a normal distribution except for the Healthcare support subscale which demonstrated skew > 2.5 at each time point.

In Rasch analysis, 14 person fit residuals exceeded the recommended range of -2.5 to +2.5 (-3.68 to 3.55); implying that approximately 6% of people gave responses not in keeping with expected scores. Scale-to-scale targeting was suboptimal. Figure 1 shows the person estimation-item location distribution for the three MyPOS subscales. The sample covers the bulk of possible item locations on the MyPOS Symptom. Some mistargeting exists for the Emotional response subscale. The scale did not cover the sample in the Healthcare support scale, indicating floor effects.

Reliability of the Myeloma Patient Outcome Scale

The Person separation indices implied good sample separation and high reliability (Table 3), except for the Healthcare support subscale consisting of only three items. This was confirmed by values of Cronbach's alpha that did not exceed a lower bound of 0.795.

Variance decomposition shows that the largest component is error variance. Next, variance is due to participants experiencing change between assessments (Table 4), reflected by high between-person variation and interaction terms for person x time and indicating that participants experienced different HRQOL trajectories over the period of eight months. The generalizability coefficients (Table 4) show that (a) reliability of screening was reasonable to good (R_{IF} 0.55 to 0.73), (b) discrimination was lower (R_{IK} <0.50), except for the Healthcare support scale, (c) test-retest reliability of the MyPOS was excellent (R_{KF} > 0.90), (d) MyPOS can reliably measure change in individual patients over time (R_C >0.60), except in the Healthcare support subscale (R_C = 0.42).

Table 4 Variance partitioning of MyPOS total and subscale scores and Generalizability reliability coefficients

Source of variance	Total MyPOS		Symptoms		Emotions and functioning		Healthcare support	
	var	%	var	%	var	%	var	%
Person	0.11	12.5	0.097	12.7	0.177	17.1	0.05	20.0
Time point	0.143	16.2	0.164	21.4	0.108	10.4	0.005	2.0
Item	0.004	0.5	0.003	0.4	0.006	0.6	0.001	0.4
Person x time point	0.2	22.7	0.178	23.3	0.202	19.5	0.021	8.4
Person x item	0.083	9.4	0.066	8.6	0.143	13.8	0.087	34.8
Time point x item	0.007	0.8	0.006	0.8	0.009	0.9	0	0.0
Error	0.334	37.9	0.251	32.8	0.393	37.9	0.086	34.4
Total	0.881	100.0	0.765	100.0	1.038	100.0	0.25	100.0
Standard error of measurement	6.9		3.2		4.9		1.1	
Scale	RIF		RIR		RKF		RC	
	Screening		Discrimination		Test-retest reliability*		Reliability of change	
Total MyPOS	0.553		0.233		0.970		0.642	
Symptoms subscale	0.587		0.218		0.974		0.680	
Emotions subscale	0.632		0.338		0.978		0.607	
Healthcare support	0.734		0.591		0.986		0.423	

*Test-retest reliability is based on patients who indicated their QOL as stable on the global rating of change.

Item invariance via DIF analysis identified the items ‘Constipation’, ‘Drowsiness’, ‘Diarrhoea’ in the Symptom subscale as unstable over time. In the Emotional response subscale, only the item ‘Worry about infections’ showed DIF. None of the items in the Healthcare support subscale showed DIF (see Supplemental Table 3).

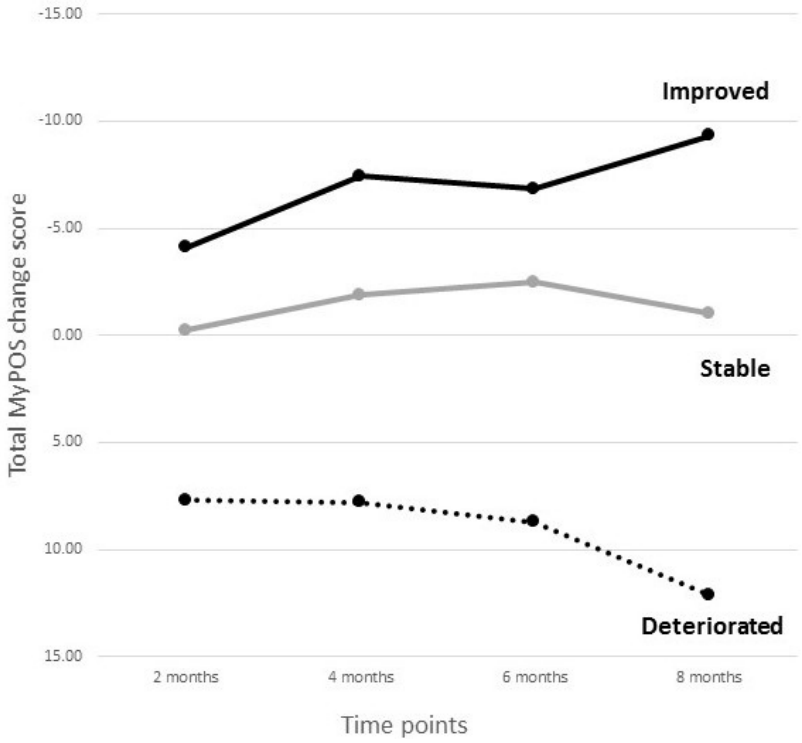
Responsiveness of the Myeloma Patient Outcome Scale

The total MyPOS score correlated moderately with the global rating scale (GRC, anchor) at every time point (range: r=0.312 to r=0.482). 125 participants contributed data for all five time points. Equal numbers of participants experienced a change in quality of life for the better or the worse, but the majority (about 60%) experienced no change (see Supplemental Table 4). Figure 2 shows the plotted change scores across time points. Except for the *Healthcare support* subscale, all mean change scores and corresponding confidence intervals indicated an improvement in MyPOS scores when patients classified themselves as overly improved, and a worsening of MyPOS scores when participants described their general quality of life as deteriorated.

Table 5 lists the optimal cut-off points (MIDs). For patients who reported they had improved, the MID for the total MyPOS score was 2.5. The subscale MIDs were 1.5 for Symptoms, 4.5 for Emotional response and 0.5 for Healthcare support. MIDs for deterioration were similar to those for improvement, with an MID of 4.5 for the total score and MIDs of 2.5, 3.5 and 0.5 for the

subscale scores. The range of MIDs is much larger derived from the distribution-based approach, with estimates ranging from a minimum of 3.4 to 13.4 in the total score and 0.3 to 9 in the subscale scores (Table 5). Further examination of mismatch between the two methods and uncertainty around the MID revealed greater misclassification for improvement than for deterioration (see distribution graph for total MyPOS, Supplemental Figure 2). The area under the ROC curve predicting improvement or deterioration was significantly greater than 0.5 ($p < 0.01$) for the total MyPOS change score and all subscale scores except the Healthcare support subscale.

Figure 2 Responsiveness of the total MyPOS change score over 8 months post baseline



Note: A negative change score on the total MyPOS denotes an improvement in quality of life

Acceptability of frequent self-monitoring for patients

46% of participants thought the MyPOS to be a feasible tool for monitoring symptoms and problems/concerns over time. 23.9% of patients did not believe it was acceptable to complete the MyPOS regularly before clinic visits. 30% of responses were missing due to drop-out at this time. Concerns about acceptability fell into two categories: (a) those who thought it unfeasible to monitor changes because their condition changed on a daily basis and a questionnaire could not capture these minute alterations; and (b) those who felt that their clinical team monitored their condition regularly and a questionnaire would duplicate information. Linked to both of these were concerns regarding overall burden, especially when receiving treatment within a clinical trial with

regular data collection, and associated cost. Positive statements included the belief that monitoring would help to focus on the symptoms and problems over time, something which these patients felt was often disregarded or overlooked in consultations: “It would help the patient to focus on their treatment, difficulties and problems. We are not always aware that some problems and side effects are related to medication and treatment and try to ignore them.” (Female participant with relapsed disease)

Table 5 Minimal important differences calculated by using mean score changes by global rating scale, Receiver-operating characteristic curve estimates and the standard deviation of baseline scores

			Mean changes by GRC		ROC analysis						Effect sizes			
		N	M_c	95% CI	Cut-off point	Sens/Spec (%)	AUC (95% CI)	p-value[g]	Sum of % misclassified	95% limit	SD[e,f]	Small[a]	Moderate[b]	Large[c]
Total MyPOS[d]											16.8			
	Improved	22/50	8.7	(3.0, 14.3)	**2.5**	77/66	0.717 (0.576, 0.858)	**0.004**	56.7%	30.9		3.4	8.4	13.4
	Deteriorated	21/50	-10.3	(-17.7, -2.9)	**-4.5**	82/57	0.719 (0.568, 0.870)	**0.004**	60.8%	18.3		-3.4	-8.4	-13.4
MyPOS Symptoms[d]											6.1			
	Improved	23/64	3.3	(0.8, 5.9)	**1.5**	65/75	0.691 (0.559, 0.823)	**0.007**	59.8%	13.5		1.2	3.1	4.9
	Deteriorated	26/64	-2.7	(-4.7, -0.7)	**-2.5**	79/57	0.687 (0.550, 0.824)	**0.006**	62.6%	6.1		-1.2	-3.1	-4.9
MyPOS Emotions[d]											11.3			
	Improved	25/59	6.1	(2.8, 9.5)	**4.5**	56/76	0.701 (0.572, 0.830)	**0.004**	67.7%	20.2		2.3	6.2	9.0
	Deteriorated	24/59	-8.0	(-13.7, -2.3)	**-3.5**	88/54	0.691 (0.544, 0.839)	**0.006**	57.7%	15.3		-2.3	-6.2	-9.0
MyPOS Support[d]											1.5			
	Improved	26/78	-0.2	(-1.1, 0.8)	**0.5**	26/80	0.565 (0.442, 0.688)	0.322	92.3%	3.7		0.3	0.8	1.2
	Deteriorated	29/78	-0.3	(-0.8, 0.2)	**-0.5**	78/27	0.544 (0.421, 0.667)	0.481	94.2%	1.8		-0.3	-0.8	-1.2

Sens: Sensitivity – proportions of patients correctly identified by the test as changed.
Spec: Specificity – proportions of patients correctly identified by the test as unchanged.
GRS: Global rating scale of change, ROC: Receiver operating characteristic, SD: standard deviation, CI: confidence interval, AUC: Area under the curve, Sum of % misclassified: [(1-Sens) + (1-Spec)].
[a]Small effect size= 0.2 x $SD_{baseline.}$; [b]Medium effect size = 0.5 x $SD_{baseline.}$; [c]Large effect size = 0.8 x $SD_{baseline}$
[d]Positive scores mean more symptoms/problems.
[e]Total sample (improved, no change or deteriorated).
[f]Standard deviation of baseline scores.
[g]Bold values indicate statistically significant Area under the curve values.

Discussion

In the CTT and Rasch psychometric analysis, the MyPOS, a disease-specific measure of quality of life and palliative care concerns in multiple myeloma, presented as having adequate construct validity and reliability for certain subscales and items. For example, in the Rasch analysis items mapped out a measurement continuum in all three subscales. In terms of suitability for longitudinal monitoring, it had excellent test-retest reliability as well as reliably measuring change and being responsive. The MyPOS was able to discriminate between subgroups of patients longitudinally. However, some symptom and health care support items with floor effects, suboptimal scale-to-scale targeting and disordered thresholds point towards areas for revision. These revisions in particular concern the third subscale, *Healthcare support*, which overall had very substantial floor effects in the items, high inter-item correlations and thus item redundancy. Further targets are items in the *Emotional Response* subscale, particularly items 15 ("Family anxiety") and 18 ("Sharing feelings with family/friends"), item 14 ("Anxiety") and item 28 ("Worry about illness worsening"), item 21 and 22 ("Usual activities"/"Hobbies") and items 19 ("Information about illness/treatment") and 33 ("Information what might happen in the future"). It is worth exploring whether the MyPOS could be shortened by removing redundant items, which might also improve model fit in the factor analysis, and whether a two-factor structure (after removal of the *Healthcare Support* items) provides a better fit to the data.

Any revisions of the MyPOS must weigh information on psychometric quality with considerations of clinical utility of the item in the clinical context [63]. Revisions need to balance considerations regarding content validity, clinical usefulness and applicability of the item and take item quality into account. A systematic review [13] identified 13 HRQOL instruments validated in myeloma, most of them generic in nature (EORTC QLQ-C30, EQ-5D and 15D, FACT-G, SF-36/12). This poses a problem as generic questionnaires do not include disease-specific concerns and symptoms and are therefore less suited for validly reflecting patient experience [18]. The MyPOS was subsequently developed following extensive patient interviews to close the gaps in item coverage identified in other HRQOL instruments, and to operationalise disease-specific HRQOL according to a conceptual model developed from these qualitative interviews [34].

We argue further that for clinical applicability, considerations of test-retest reliability and responsiveness to change for enabling the valid monitoring of patients in clinical practice are paramount. However, this information is often not available for disease-specific tools in multiple myeloma. For example, an MID was only determined for the EORTC QLQ-C30 and the two health state measures EQ-5D and 15D [58,59]. Subsequently, two new disease-specific tools, the MDASI-MM [60] and the FACT-MM [61], have been developed, but their validation has not yet been completed or has not included longitudinal validity testing to date. Another aspect lacking

from validation studies is the investigation of scaling quality. One notable exception is a study exploring Mokken scaling stability of the EORTC QLQ-C30 across different subpopulations of myeloma [62]. However, this analysis did not provide in-depth information on each item and did not look at item stability in a longitudinal context. For the MyPOS we provide both information on scaling quality and longitudinal validity.

Regarding possible revisions of the MyPOS, the measurement aim needs to be considered. For example, floor effects in gastrointestinal symptoms may be observed for most of the sample of a relatively stable myeloma population not currently undergoing anti-cancer treatment or receiving maintenance treatment only [79]. However, they are important symptoms to monitor for the clinician to make adjustments to the treatment plan should they suddenly become severe [69-71,86]. Inspection of the person-item threshold maps shows that it is not the items in the measure that do not cover the whole spectrum but rather the sample that did not target all the item difficulty locations. Similarly, floor effects are commonly seen in HRQOL and health satisfaction measures that are constructed with the intention of being applicable to a wide range of disease severity levels [64-66]. This is even true for disease-specific scales and was observed in the field-testing of the EORTC QLQ-MY24 [67], subsequently revised to 20 items. Floor effects in healthcare support items may reflect the finding that respondents have more positive experiences with the healthcare they received affecting their willingness to participate in studies from the outset [68]. However, while revision of the scale helped improve the fit of items in the *Symptoms* and *Emotional Response* subscale, the *Healthcare Support* subscale remained to have very poor fit. Removal of this subscale might help improve overall fit of the MyPOS.response scale adaptations should be performed after further qualitative, cognitive interview work [57,72]. Another option is to extend the range of item difficulties to cover all levels of severity and impact of myeloma on HRQOL by constructing item banks and computer adaptive testing [73].In our analysis we tried to combine the perspectives of traditional psychometric approaches (confirmatory factor analysis, responsiveness and MID) with modern item response theory for evaluating the stringent criteria proposed by McHorney *et al* [23] for longitudinal individual patient monitoring. Using the new approaches addresses shortcomings of CTT such as validating only total scores instead of single items in a measure and yielding sample-dependent results [29]. The benefits of Rasch analysis include item-level statistics and information on how items can be improved to fit the application in a specific sample [35]. Furthermore, generalizability theory [26-28] allows an exploration of sources of variation in item scores, which leads to establishing various reliability indices to distinguish different scenarios of use, i.e. using HRQOL measures for screening (single application) or for monitoring (application to track outcomes over time in an individual). This extends the limited exploration of test-retest reliability in CTT approaches [22]. The new psychometrics are proposed as extensions to the original operationalisations of

measurement quality criteria that were proposed by McHorney et al [23] in their seminal paper. They can potentially offer additional information on sources of floor & ceiling effects and, due to Rasch analysis yielding information on the full range of the construct being measured, sources of problems with the coverage of constructs and diverse patient groups. The same is true for Generalizability analysis that provides a fine-grained picture of sources of measurement error beyond the random measurement error and can therefore help understand problems with precision of measurement in the cross-sectional and the longitudinal application [27,28]. However, especially the latter approach to reliability assessment and the indices proposed by Cranford et al [46] are limited by not being used widely in the literature which makes their interpretation difficult. For example, it is not clear whether thresholds for acceptable ICC estimates as proposed by McHorney et al [23] are applicable for the screening, discrimination and reliable change index proposed in this paper [46]. Further research is needed to explore this issue. Moreover, we used Cranford et al's [46] method in a situation of a less intensive longitudinal design, with far less frequent measurement than was employed in their diary study. Therefore, the analysis of sources of variation stemming from different time points is not as detailed as in their original analysis.

Applying the framework of quality criteria for individual patient-monitoring to the MyPOS yields the following assessment of its suitability for this application. Regarding (i) practical features, survey administration is well below 15 minutes [15], however, the number of items is rather high for a clinically applicable tool [18]. The analysis of breadth of health measured (ii) yields good dimensionality of the measure and coverage of all aspects of disease-related QOL according to the theoretical model [15], however, scale revisions indicated by low factor loadings, item redundancy and poor fit of the *Healthcare Support* subscale call for further exploration of dimensionality. Criterion (iii), the depth of health measured, was partially fulfilled with floor effects showing in 10/33 items and person-item targeting analysis within Rasch modelling suggesting further analysis in more severely affected samples. Criteria (iv) and (v) pertaining to reliability were assessed slightly differently by extending suggested analyses of Cronbach's alpha for cross-sectional reliability and test-retest reliability by Rasch analysis and Generalizability theory, and by omitting standard error of measurement as a quality criterion. Although the actual size of the coefficient that should be obtained is unclear, the rigorous criterion for reliability (>0.95) set by McHorney et al [23] was achieved for all subscales in longitudinal analysis, but not for cross-sectional reliability (screening & discrimination application, Cronbach's alpha). Validity (vi) in terms of cross-sectional construct validity and responsiveness to change yielded good sensitivity to change values. Further convergent and divergent validity assessment is reported in the initial validation of the MyPOS [15].

One of the most important features that makes a scale suitable for monitoring purposes is its responsiveness to change [19]. Our MIDs for improvement and deterioration were smaller than

the MIDs reported by Kvam and colleagues for the EORTC QLQ-C30 for patients with multiple myeloma [59]. Their MIDs range from 6-17 points for improvement and 12-27 points for deterioration, a small to medium change [59]. This discrepancy might arise from the different nature of the QLQ-C30, a generic measure, with absolute higher values of meaningful change [74-77]. The large baseline standard deviations and the amount of misclassification that was seen imply that not enough patients in our sample experienced a substantial change and that there further exists imprecision in the anchor in classifying participants into improved and deteriorated. This is a commonly reported problem with the ROC-curve based method of MID [49,78] which, as a diagnostic approach, would require a bias-free and precise gold-standard anchor. However, in the absence of guidance regarding construction of global rating scales this situation might not easily be rectified.

The first limitation of our study is the use of consecutive enrolment, resulting in a convenience sample. The strength lies in its greater clinical representativeness that counteracts the effect of sampling younger and fitter patients if validation is part of a clinical trial [79,80]. However, since we recruited from outpatient clinics or day centres, we potentially missed patients feeling too unwell to participate in a longitudinal survey. This was the first study to use Generalizability theory. This approach for evaluating sensitivity to change normally requires frequent assessments [46]. However, due to patient burden this was not feasible. The reliability coefficients may be an underestimation of the true longitudinal reliability of the MyPOS. Furthermore, since this approach is relatively new, there are no guidelines as to the size of the coefficients. Confirmatory factor analysis used the DWLS approach to account for non-normality and the ordinal nature of the response scale in the MyPOS. However, although this approach has been reported as robust in samples of above 200, a caveat is its use in situations were missing data is missing not at random [85]. Baseline data was used for confirmatory factor analysis with missingness likely not due to systematic item nonresponse or non-random mechanisms. However, low factor loadings of some items might be due to systematic bias, i.e. for item 24 “Worry about sex life”, with effect on model fit. Different groupings of functioning items on subscales in the reported factor analysis compared to the initial factor analysis reported in Osborne et al. [15] are most likely due to changing descriptive labels of the rating scale of the symptom items to adapt the MyPOS to the overall item and scaling format of the IPOS [31], of which it is a module. In the adapted version of the MyPOS, the rating scale for the symptoms only lists the severity of impairment but not the added descriptor “impaired activity or concentration”. This change might have affected other aspects of construct validity, which likely necessitates a re-validation of aspects of construct validity of the symptom subscale. For the anchor-based MID approach, there is no consensus for the amount of categories and the exact phrasing of the global rating scale of change. Authors have used 3-point [83] to 15-point scales [81]. We tried to balance the potential lack of sensitivity of

fewer response options with the need to arrive at a valid measurement of change presenting only so many levels which patients can adequately discriminate. Since we asked patients to compare a change in their condition always to the first assessment, recall bias may have affected at least part of the sample. Furthermore, the wording of the rating scale might not present a valid global assessment of change in quality of life as operationalised in the multi-dimensional, disease-specific MyPOS. The validity of the global rating of change as a criterion for anchor-based derivation of the MID is further pulled into question by the relatively low correlation between anchor and change scores and the MID not exceeding the SEM in all subscales.

Conclusion

This analysis supported the responsiveness and test-retest reliability of the MyPOS, using a multi-centre outpatient sample of patients at different disease stages. Additional derivation of the MID for use in individual patient care and exploration of valid anchors of global change are needed. Modifications to the scoring format and potential removal of the Healthcare Support subscale may be warranted, subject to further testing. The study was the first to apply Generalizability theory to establish test-retest reliability and stability of scores in frequent measurements in medicine.

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Conflicts of interest

All authors declare that they have no conflicts of interests.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Ethical and research governance approvals were obtained from the Central London Research Ethics

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Informed consent

Informed consent was obtained from all individual participants included in the study.

Author's contributions

CR detailed methods for the study, led the application for ethical approvals, collected the data, planned and conducted the data analysis and drafted the manuscript, supervised by IJH, GW and RJS. IJH led the application for funding for this programme of work, which included this study, in collaboration with SAS, RJS and PME, and acted as senior researcher overseeing the project and publications. All authors contributed to the preparation of the manuscript and read and approved the final manuscript.

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SUPPLEMENTAL MATERIALS

Longitudinal validity and reliability of the Myeloma Patient Outcome scale was established using traditional, generalizability and Rasch psychometric methods

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Supplemental Table 1 Factor loadings of the MyPOS and fit statistics for confirmatory factor analysis

Item no.	Description	Symptoms	Emotions	Support
1	Pain	.638		
2	Shortness of breath	.529		
3	Fatigue	.697		
4	Nausea	.563		
5	Vomiting	.451		
6	Appetite loss	.629		
7	Constipation	.532		
8	Mouth problems	.442		
9	Drowsiness	.645		
10	Poor mobility	.695		
11	Diarrhoea	.333		
12	Tingling	.358		
13	Remembering	.560		
14	Anxiety		.772	
15	Family anxiety		.614	
16	Depression		.715	
17	At peace		.775	
18	Sharing feelings		.480	
19	Information		.457	
20	Practical matters		.397	
21	Usual activities		.674	
22	Hobbies		.686	
23	Quality time		.670	
24	Sex		.149	
25	Infections		.392	
26	Appearance		.495	
27	Finances		.374	
28	Illness		.704	
29	Coping		.773	
30	Advice			.616
31	Knowledge			.877
32	Care and respect			.851
33	Future		.383	
	Variance explained	28.1%	7.2%	6.9%
Confirmatory factor analysis				
χ^2 p-value		<0.0001		
χ^2/ df		2.213		
CFI (>0.90)		0.794		
NFI (>0.95)		0.682		
NNFI (>0.95)		0.779		
RMSEA (95% CI) (<0.06)		0.073 (0.067-0.078)		

Abbreviations: CFI, comparative fit index; df, degrees of freedom; NFI, normal fit index; NNFI, non-normal fit index; RMSEA, root mean square error of approximation; MyPOS, Myeloma Patient Outcome Scale.

Note: Thresholds for fit indices are indicated in brackets.

Supplemental Table 2 Rasch model fit for each subscale with item and person location fit statistics

Measurement characteristic	**Symptom subscale (13 items)**	**Emotional response subscale (17 items)**	**Healthcare support subscale (3 items)**
Item locations			
Mean (SD)	0 (0.858)	0 (0.348)	0 (0.774)
Range	-1.16 to 1.92	-0.69 to 0.41	-0.69 to 0.83
Thresholds			
Range	-2.49 to 5.62	-2.19 to 1.86	-3.07 to 5.28
Fit residuals: Mean (SD)	-0.102 (1.191)	0.175 (1.66)	0.170 (0.338)
Skewness	0.812	0.353	-0.221
Person measures			
Mean (SD)	-1.824 (1.101)	-1.195 (1.058)	-4.086 (1.484)
Range	-4.89 to 0.63	-4.33 to 0.69	-4.74 to 8.42
Fit residuals: Mean (SD)	-0.203 (0.875)	-0.159 (1.163)	-0.183 (0.621)
Skewness	0.345	-0.176	-0.146
Person separation index	0.804	0.834	0.127
Overall fit			
X^2	65.651	143.74	11.887
p-value	0.005	0.001	0.065
RMSEA (90% CI)	0.054 (0.038, 0.067)	0.088 (0.074, 0.100)	0.064 (0.049, 0.076)

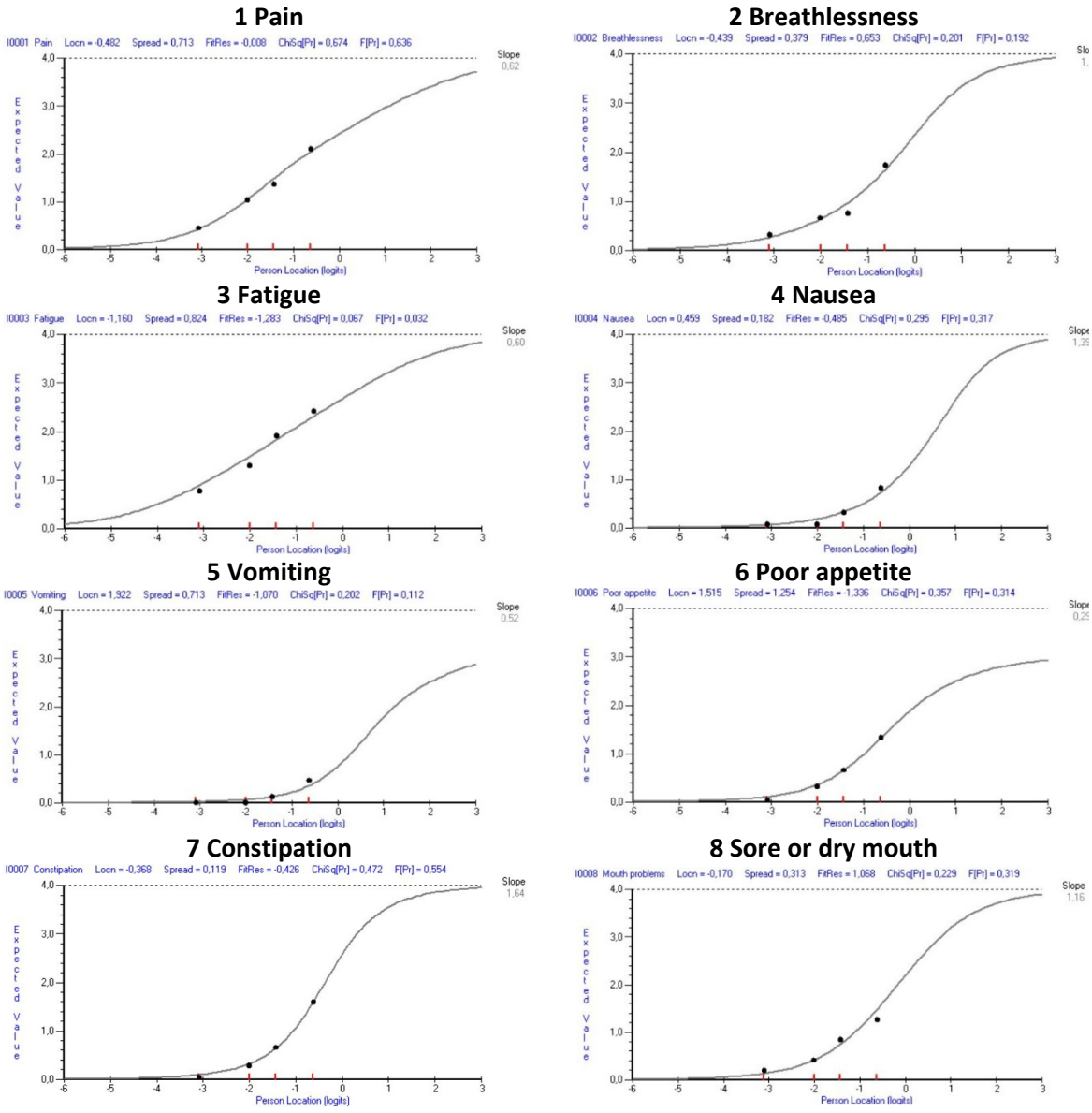
Note: RMSEA was calculated according to the formula $\sqrt{\text{Max}}([(X^2/df)-1/(N-1)], 0)$ [82].
Abbreviations: CI, confidence interval; sd, standard deviation; RMSEA, root mean square error of approximation.

Supplemental Table 4 Changes in scores between baseline and assessments 2, 3, 4 and 5 for the total MyPOS score and its subscales. Presented are mean change scores and the standard deviation of changes.

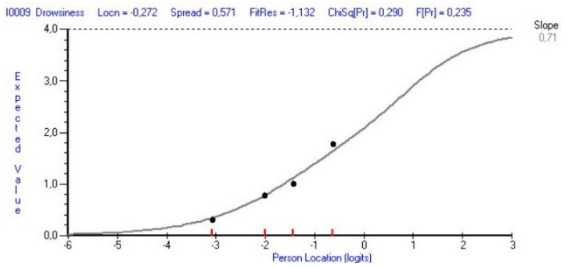
	Change TP1-TP2			Change TP1-TP3			Change TP1-TP4			Change TP1-TP5		
MyPOS Total Score												
My QOL has…	**n**	**M_c**	**SD_c**	**n**	**M_c**	**SD_c**	**n**	**M_c**	**SD_c**	**n**	**M_c**	**SD_c**
Improved	14	5.7	10.7	22	8.0	9.3	16	9.6	13.3	22	8.7	13.5
No change	90	0	10.1	69	2.3	9.5	64	1.9	11.2	50	0.9	7.6
Got worse	11	-8.4	6.9	13	3.8	13.4	21	-8.2	14.5	21	-10.3	17.4
Missing	84	-7.6	19.7	67	-6.2	9.6	49	-3.1	11.5	32	-7.5	11.3
Rho*	0.33			0.40			0.40			0.45		
MyPOS Symptom subscale												
	n	**M_c**	**SD_c**	**n**	**M_c**	**SD_c**	**n**	**M_c**	**SD_c**	**n**	**M_c**	**SD_c**
Improved	15	2.5	6.9	25	2.8	5.8	20	2.6	4.3	23	3.3	6.2
No change	116	-0.2	4.2	90	1.0	3.9	74	1.0	5.0	64	0.2	3.6
Got worse	17	-3.5	4.7	17	-2.2	5.2	30	-2.5	5.4	26	-2.7	5.3
Missing	51	-2.0	8.6	39	-2.5	4.5	26	-1.7	5.2	12	-3.5	6.1
Rho	0.26			0.27			0.31			0.40		
MyPOS Emotional response subscale												
	n	**M_c**	**SD_c**	**n**	**M_c**	**SD_c**	**n**	**M_c**	**SD_c**	**n**	**M_c**	**SD_c**
Improved	18	2.4	8.0	26	4.7	6.4	19	5.4	9.2	25	6.1	8.6
No change	109	0.6	7.5	84	1.4	7.2	71	1.0	8.2	59	0.8	5.9
Got worse	14	-5.0	5.8	15	-2.6	10.6	23	-5.7	10.5	24	-8.0	14.2
Missing	58	-4.2	10.5	46	-2.8	6.3	37	-1.6	8.9	17	-3.5	6.1
Rho	0.20			0.28			0.35			0.41		
MyPOS Healthcare support subscale												
	n	**M_c**	**SD_c**	**n**	**M_c**	**SD_c**	**n**	**M_c**	**SD_c**	**n**	**M_c**	**SD_c**
Improved	19	-0.1	0.4	27	0.2	0.9	24	0	0.7	26	-0.2	2.3
No change	137	0.2	2.0	107	0.3	1.8	85	0.3	2.1	58	0.1	2.3
Got worse	20	-0.8	1.4	19	-0.3	1.6	31	-0.3	1.1	29	-0.3	1.3
Missing	23	-0.1	1.4	18	-0.2	0.7	10	0.1	0.5	12	0.1	0.3
Rho	0.16			0.12			0.14			0.14		

*Spearman's Rho shows the correlation between the change scores and the anchor at each time point. The correlation between the global change rating and the baseline values were: 0.66 (Total MyPOS), 0.23 (Symptoms subscale), 0.59 (Emotional response subscale), and 0.24 (Healthcare support subscale). **Abbreviations:** Mc, mean change score; SDc, standard deviation of change score; QOL, quality of life; MyPOS, Myeloma Patient Outcome Scale; TP, time point.

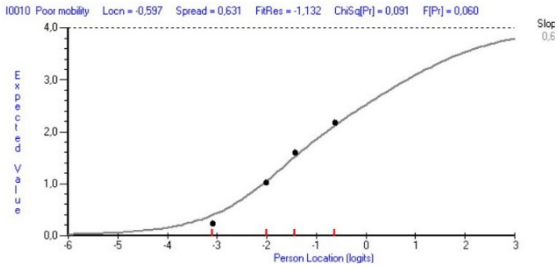
Supplemental Figure 1 Item characteristic curves for all 33 MyPOS items
Item characteristic curves plot responses predicted by the Rasch model (curve) and observed responses for all the different levels of quality of life and palliative care concerns in multiple myeloma (the measurement continuum). The available responses are 0 ‘not at all‘, 1 ‘slight‘, 2 ’moderate‘, 3 ’severe‘ and 4 ‘overwhelming‘. The observed mean scores are plotted according to levels of quality of life with the participants with the lowest quality of life represented on the left-hand side and those with the highest observed level of quality of life represented on the right-hand side. Poor graphical fit to the Rasch model is apparent when the plotted observed means (dots) do not follow the continuous line. Items 12 ‘Tingling in the hands/feet‘, 24 ‘Worry about sex life’ and 33 ‘Information about future’ show a slight under-discrimination (also indicated by the positive fit residual for these items which is >2.5), in which participants with a higher level of quality of life report more difficulty with these areas than would be expected by the Rasch model, and participants with a lower quality of life report less difficulty with these items than would be expected.



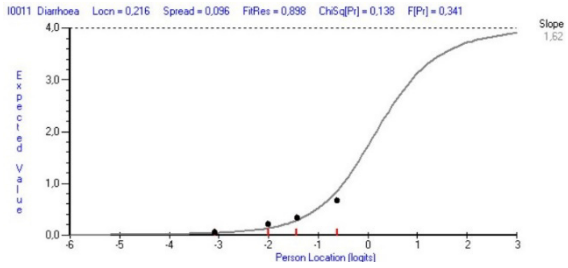
9 Drowsiness



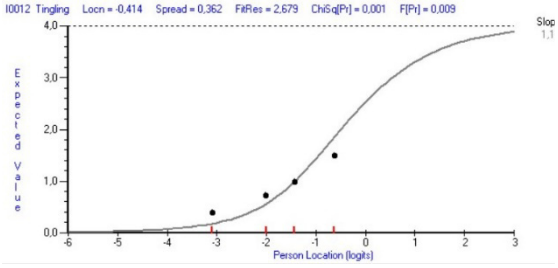
10 Poor mobility



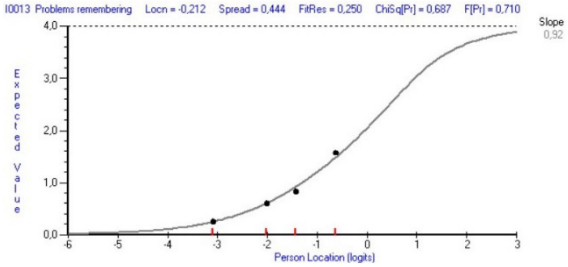
11 Diarrhoea



12 Tingling in hands/feet

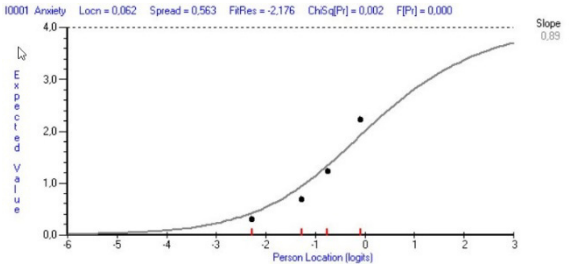


13 Difficulties remembering

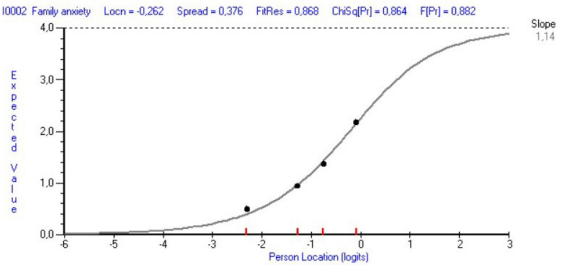


SUBSCALE EMOTIONAL FUNCTIONING

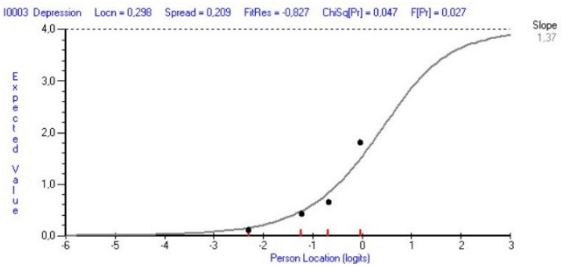
14 Anxiety



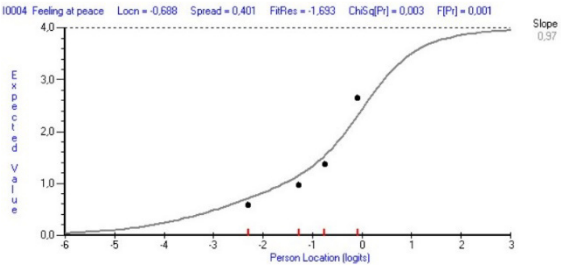
15 Family anxiety



16 Depression

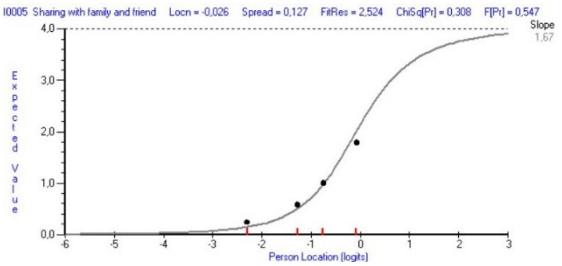


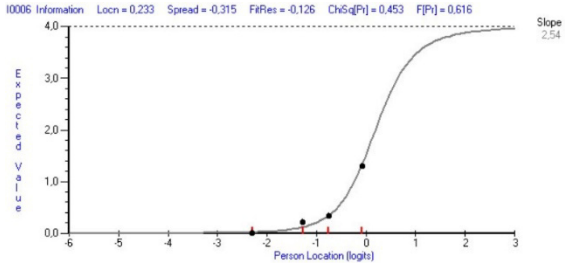
17 Feeling at peace



18 Sharing with family/friends

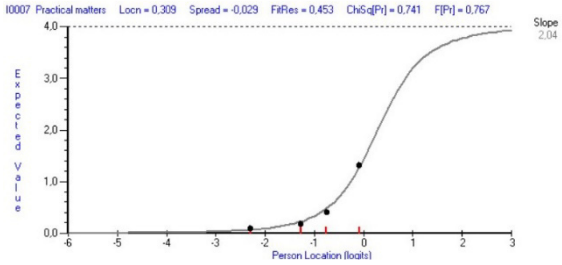
19 Information

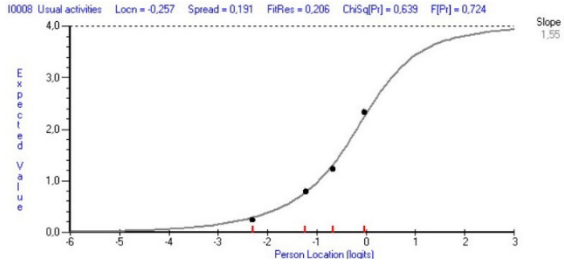




20 Practical matters

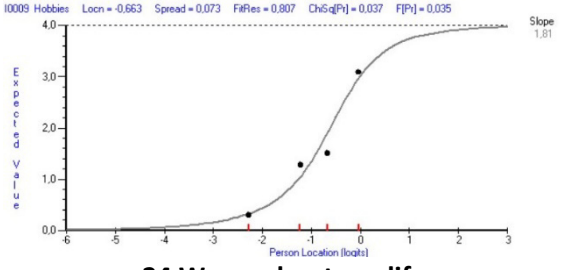
21 Usual activities

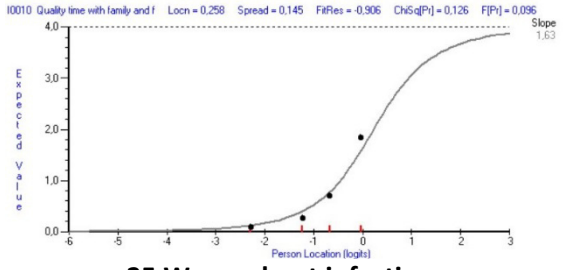




22 Hobbies

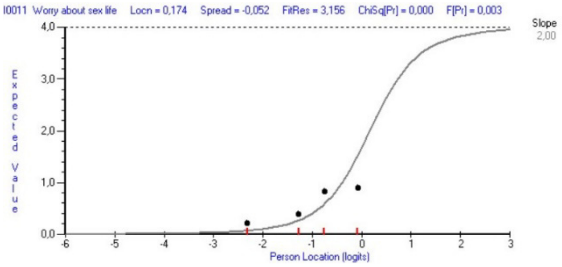
23 Quality time

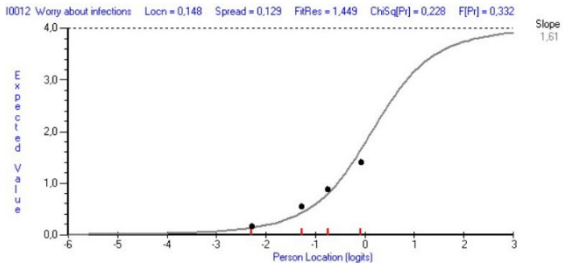




24 Worry about sex life

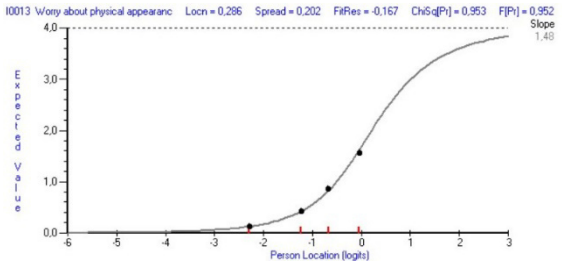
25 Worry about infections

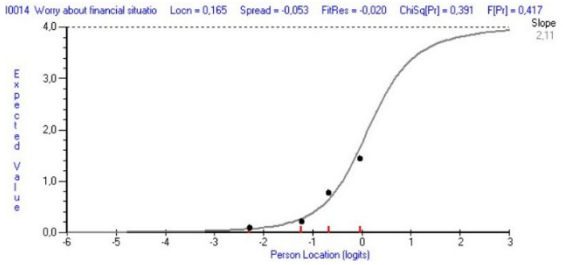




26 Worry about physical appearance

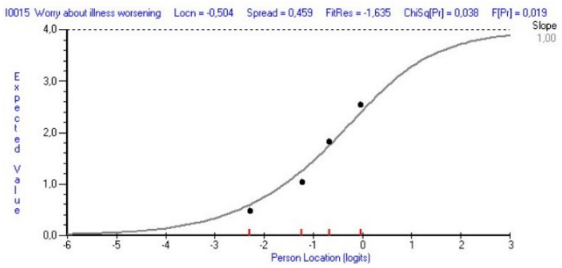
27 Worry about finances

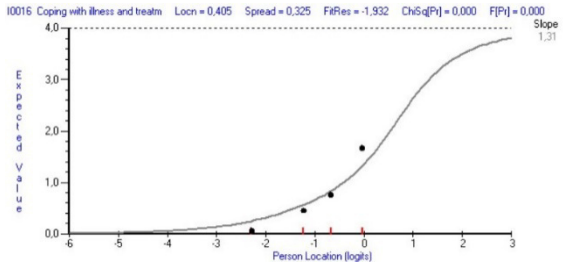




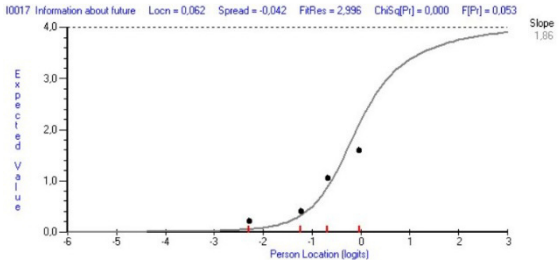
28 Worry about illness worsening

29 Coping with illness/treatment



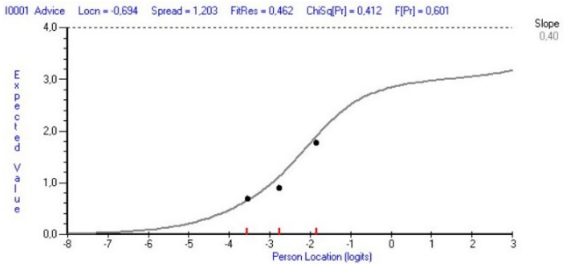


33 Information about future

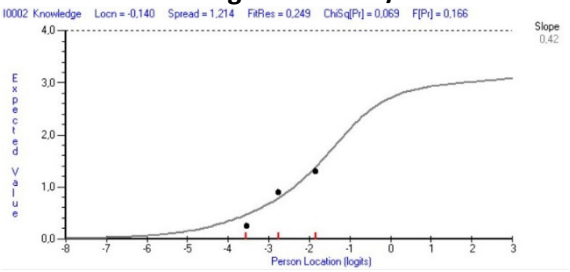


SUBSCALE HEALTHCARE SUPPORT

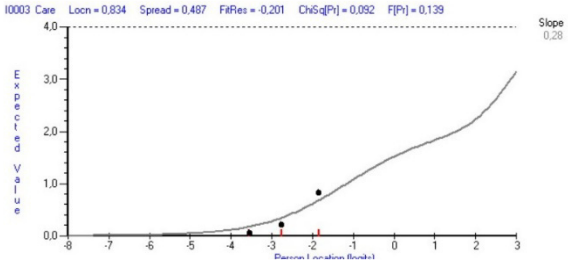
30 Advice from doctors/nurses



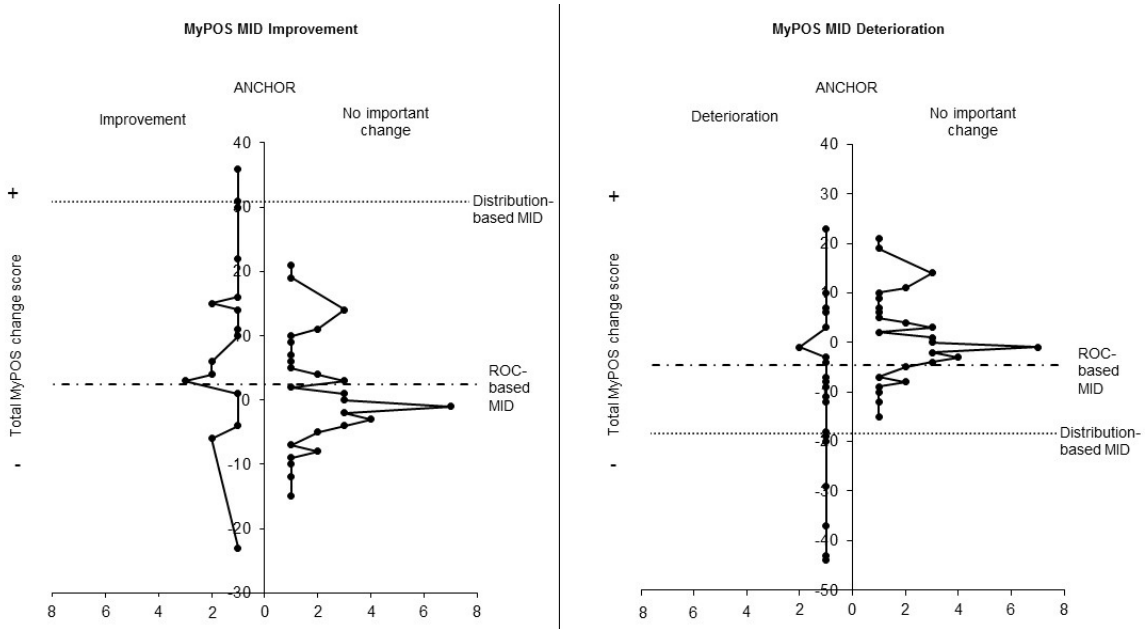
31 Knowledge of doctors/nurses



32 Doctors/nurses show care/respect



Supplemental Figure 2 Distribution (expressed in percent) of changes in scores on the total Myeloma Patient Outcome Scale for patients with multiple myeloma who report an important improvement (left-hand side) or an important deterioration (right-hand side) in their quality of life compared to those who reported no important change at time point 5. The ROC point indicates the ROC-based MID, the 95% limit indicates the distribution-based MID that was determined.



8 Integration of findings and discussion

8.1 Integration of findings

This thesis presents some of the first evidence relating to the symptom burden and palliative care concerns over time in patients with multiple myeloma. It therefore addresses the gap of insufficient longitudinal data on HRQOL in this patient group, focusing in particular on those patients with advanced disease. By using a new statistical method of analysing trajectories it was possible to understand the considerable heterogeneity in changes in HRQOL in multiple myeloma and to identify a group of patients that experienced deteriorating or poor QOL. The six factors general symptom burden, presence of severe fatigue and pain, poor ECOG performance status (ECOG group 2 or higher) and presence of clinically relevant anxiety and depression were identified as baseline predictors of poor or deteriorating QOL.

For the monitoring of individual symptom burden and QOL over time, a newly developed myeloma-specific questionnaire was used, the MyPOS. The second aim of this thesis was to test its validity, reliability and acceptability for monitoring symptom burden and palliative care concerns, thereby not only describing these aspects over time but developing ways of tracking changes in these outcomes validly and reliably, so that the measure can be used in routine clinical practice. This thesis is unique in investigating the question of longitudinal monitoring both from a measurement/psychometric and a prognostic research perspective. Particularly regarding the properties that show suitability of an instrument for longitudinal monitoring, this work proposed and investigated a set of new psychometric criteria. By integrating the findings from the longitudinal QOL study with information on the psychometric quality of the measure for this application, it is possible to build a model of factors with prognostic value, thereby allowing the identification of variables and items that are targets for monitoring.

It is proposed that these variables can indicate who would benefit from palliative care and possibly early integration of palliative care. As was shown in the introduction (section 2.1.3), haematological cancer patients are often seen late in their disease trajectory or not referred at all to specialist palliative care services. Ultimately, the clinical implication of the evidence is that for early referral to palliative care, a paradigm shift from prognosis/survival models to models of need incorporating PROs needs to happen in multiple myeloma care. Only routine monitoring of symptom burden and QOL-related aspects can help identify those needs. At the end of this chapter, these implications are discussed in detail. The following sections present some more in-depth discussion of aspects that were not reviewed in the articles presented as chapters 5, 6 and 7 of this thesis. I then focus on the methodological discussion of strengths and weaknesses of this

research and suggest ways of applying the findings in clinical research, and in haematological and palliative care clinical practice.

8.1.1 Symptom burden and trajectory of palliative care problems in multiple myeloma

The first three objectives of this study centred on assessing symptom severity, palliative care concerns and health-related quality of life in patients with multiple myeloma both cross-sectionally and longitudinally. Determining which factors were associated with a poor or declining HRQOL was part of both studies, first building a model of predictors in a secondary analysis of a large sample involving data from the initial validation study of the MyPOS and the baseline data from the longitudinal survey. This model of predictors was refined and validated in the longitudinal survey, showing a stronger influence of symptom-related than disease- or treatment-related factors.

Observational research, particularly research involving patients with advanced disease at relapsed or refractory stages, is rare in multiple myeloma. In the systematic review of QOL evidence in myeloma (see chapter 2.2.2.3), only a handful of genuine observational studies employing a population perspective and aiming to describe QOL in this population could be located. Most of these studies are cross-sectional in their design and involve mixed samples. Four recent studies, one involving 154 outpatients with multiple myeloma (598), one focusing in particular on the influence of length of stable disease phase on disease- and treatment-related symptoms (83), and one involving survey data of myeloma patients and their main caregivers sampled through Myeloma UK (90), provide a perspective on QOL that is not defined by a specific anti-myeloma or supportive care treatment that is tested in a clinical trial. Additionally, Boland's study (2013) (593), albeit its small sample size (n=32), represents the only study including advanced patients, therefore presenting data applicable to the palliative care sector. Despite multiple myeloma now being a disease characterised by a long and chronic disease trajectory (62,73,692,693), providing opportunities to monitor QOL over time as patients progress through treatment lines and treatment-free intervals (and thus sharing characteristics of the typical trajectory of non-cancer conditions such as chronic obstructive pulmonary disease or heart failure (157,694)), longitudinal changes in the QOL of myeloma patients are seldom described. Mols et al. (2012) (381) coupled a QOL survey with registry-based monitoring but used only two measurement time points, one year apart. The remaining evidence stems from studies using samples of SCT patients that are usually followed over the period of one year (31,35,36,490,695,696), with one exception of monitoring for 36 months (31). However, since SCT is first-line treatment in those under the age of 75

(75,96,697), these studies do not represent the wider myeloma population because they involve mainly younger and fitter patients with less advanced disease (145,698).

The general symptom level of myeloma patients varies widely, depending on sample characteristics. In this cross-sectional study, patients reported a mean of 7.2 out of 15 potential symptoms on the MyPOS, with one third of the sample reporting 6 – 8 symptoms and nearly 40% being highly symptomatic with 9-15 symptoms. These proportions did not change much over the study period of eight months. The mean number of symptoms was much higher than in the general population which reports a median of 3-4 symptoms (699). It was higher than in a cross-sectional study of mixed haematological cancer patients, including 54 individuals with multiple myeloma, in which a mean number of 5.6 symptoms was reported, 2.3 of which were severe (9), and a similar study in a smaller sample (700). The fact that this sample was composed of a third of advanced patients is also apparent when comparing the proportion of moderately and severely symptomatic patients to Jordan et al.'s (2014) (598) sample composition. While the percentage of moderately symptomatic patients is comparable to Jordan's study (598), the percentage of severely symptomatic patients exceeds the proportion in their sample by 10%.

A more fine-grained comparison of how the findings from this study relate to the available research on symptom prevalence in multiple myeloma is provided in Table 7. Here, results from this survey are compared to the point prevalence and confidence intervals determined in the meta-analysis presented in chapter 2.2.2.1. In comparison to all studies in myeloma and mixed haematological cancer populations, the most striking differences in symptom prevalence existed for pain, breathlessness and gastrointestinal symptoms. Pain with a prevalence of 70.8% in this study was much higher than the pooled prevalence ascertained in the meta-analysis (44.5%, 95% CI 34.4 to 54.9%). The difference was even higher for breathlessness. Here, we found almost twice the prevalence than in the systematic review (60.2% versus 32.6%, respectively). A marked higher prevalence of gastrointestinal symptoms (constipation, appetite loss, diarrhoea), however, was reported in the systematic review. This difference probably reflects the divergent composition of the sample, with a comparably smaller proportion of patients being on active chemotherapy or anti-cancer treatment and a far smaller proportion of patients undergoing haematopoietic stem cell transplantation (HSCT) in this study. Gastrointestinal symptoms are common side effects of these treatments (701). The prevalence of fatigue, on the contrary, was again higher in this study than in the review (59.3% compared to 86.8% in this study). The proportion of patients with severe fatigue is also twice as high as the pooled estimate in the systematic review (59% versus 20.7%). These marked differences, together with the slightly higher prevalence of memory problems and the much higher prevalence of breathlessness in this sample point towards age and comorbidity as possible influencing factors. Elderly people in general are more likely to report comorbid conditions. In the case of multiple myeloma, lung impairment can be a consequence of disease-

related processes or secondary to treatment (207). It has been shown to be an important risk factor for mortality, possibly confounded by poor functional status (206,207,209,702). This also shows that the sample recruited in this study is different from clinical trial samples on which the prevalence estimates from the systematic review are based.

Table 7: Comparison of prevalence of symptoms to MyPOS-reported prevalence* (point prevalence and 95% confidence intervals)

Symptoms	This study	n	Prevalence review
Pain	70.8 (67.0 – 74.6)	1882	44.5 (34.4 – 54.9)
Severe pain	46.3 42.1 – 50.4)	1136	25.9 (18.2 – 35.6)
Breathlessness	60.2 (56.1 – 64.3)	245	32.6 (17.9 – 51.8)
Severe breathlessness	27.3 (23.6 – 31.0)	253	25.1 (5.0 – 67.9)
Fatigue	86.8 (83.9 – 89.6)	1204	59.3 (44.8 – 72.3)
Severe fatigue	59.0 (54.9 – 63.1)	620	20.7 (11.1 – 35.4)
Nausea/Vomiting	28.9 (25.1 – 32.7)	981	13.3 (3.2 – 41.5)
Severe nausea/vomiting	11.4 (8.8 – 14.0)	245	9.2 (0.5 – 66.9)
Appetite loss	16.0 (12.9 – 19.1)	770	23.1 (11.4 – 41.1)
Severe appetite loss	7.3 (5.1 – 9.5)	245	25.7 (6.5 – 63.2)
Constipation	38.0 (33.9 – 42.0)	639	39.1 (24.3 – 56.3)
Severe constipation	17.3 (14.2 – 20.4)	245	21.3 (9.0 – 42.5)
Mouth problems	36.9 (32.9 – 41.0)	1047	22.5 (13.8 – 34.5)
Severe mouth problems†	13.7 (10.8 – 16.6)	154	17.1 (1.4 – 35.6)
Drowsiness	26.2 (22.6 – 29.9)	308	32.5 (14.0 – 58.9)
Severe drowsiness	10.7 (8.1 – 13.3)	-	-
Poor mobility ††	70.8 (67.0 – 74.6)	1424	43.2 (33.3 – 53.6)
Severely decreased	48.1 (44.0 – 52.3)	245	8.6 (2.8 – 24.0)
Diarrhoea	23.0 (19.5 – 26.5)	805	9.5 (2.1 – 33.9)
Severe diarrhoea	9.3 (6.9 – 11.7)	245	15.3 (1.4 – 70.3)
Tingling in hands/feet	54.2 (50.1 – 58.3)	451	42.7 (29.0 – 57.7)
Severe tingling	27.5 (23.8 – 31.2)	154	32.0 (10.8 – 53.1)
Problems remembering	55.8 (51.7 – 59.9)	281	37.0 (21.3 – 55.9)
Severe problems	21.6 (18.2 – 25.1)	-	-
Case of anxiety	13.9 (11.0 – 16.8)		26.4 (19.1 – 35.3)
Case of depression	11.9 (9.2 – 14.6)		20.8 (13.4 – 31.0)

*Pooled prevalence rates are reported in a meta-analysis, see background section, page 65
†Only one study
††Item only included in MyPOS, comparable to items of physical functioning, therefore compared to physical functioning subscales

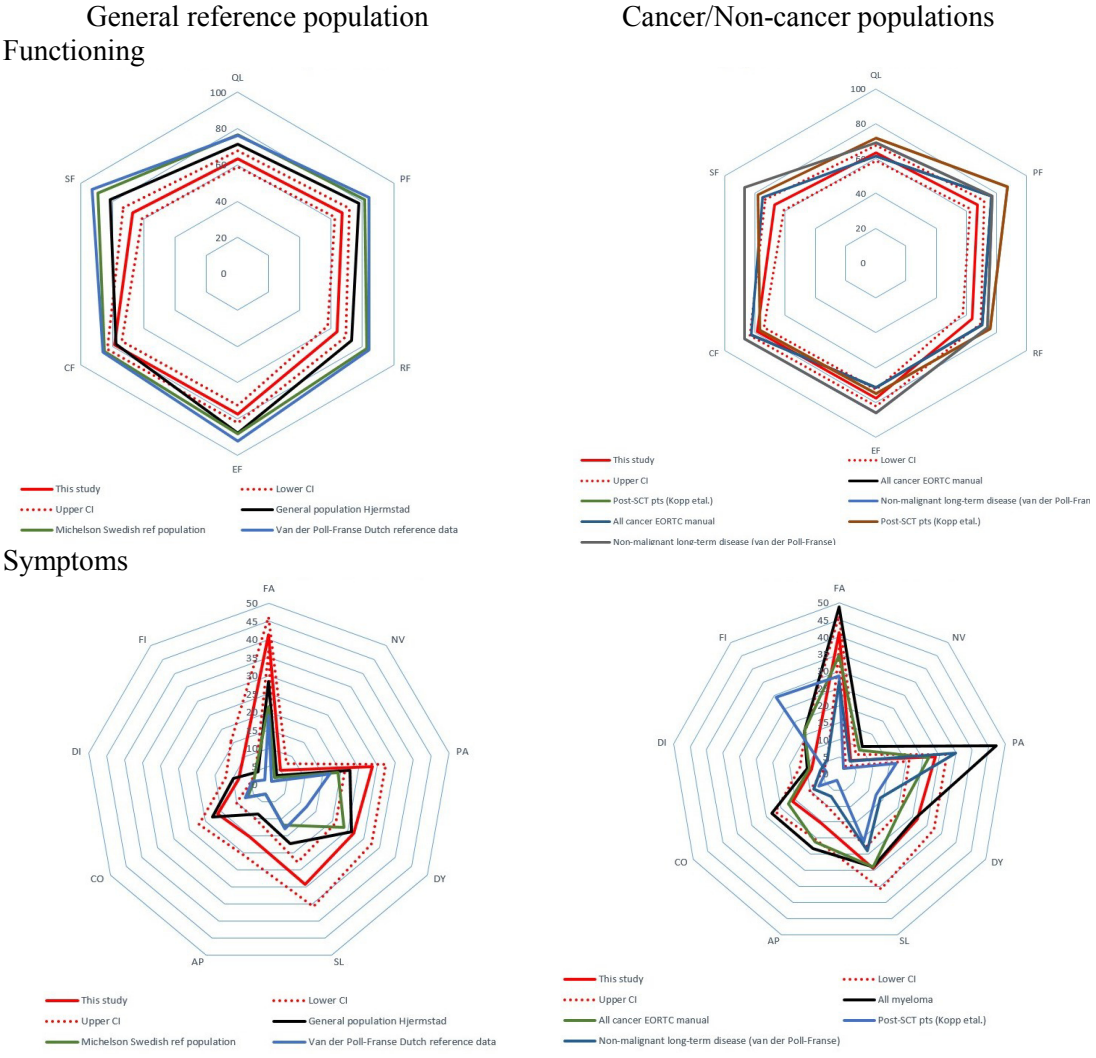
Overall, when comparing results of this study to the wider literature, the type and prevalence of symptoms in this study closely resembled that of previous reports. However, the pattern of symptom prevalence was different. In the meta-analysis, the most prevalent symptoms were fatigue, pain, poor mobility, tingling in the hands/feet (peripheral neuropathy) and constipation. The top five prevalent symptoms in this study were fatigue 86.8% (95% CI: 83.9-89.6%), pain 70.8% (67-74.6%), poor mobility 70.8% (67.0-74.6%), breathlessness 60.2% (56.1-64.3%), and

problems remembering 55.8% (51.7-59.9%). Tingling in the hands/feet placed sixth with a prevalence of 54.2%. These results do not differ greatly from general reviews of symptom burden in non-cancer conditions, solid tumours and particularly advanced cancer. The triad pain, breathlessness and fatigue, for instance, has been found in well over 50% of both cancer and non-cancer conditions at the end of life (703). These symptoms are thus considered universal. The estimates in multiple myeloma are well comparable to the solid cancer population (484,566,704,705). Particularly the high prevalence of pain and breathlessness is comparable to rates reported in the very advanced and palliative cancer population (122,536,566,705). These findings underscore the considerable burden of myeloma patients that is not confined to the later stages of disease, but already apparent in newly diagnosed patients. Particularly the high prevalence of pain is striking since the lower use and lower referral rates to palliative care services (151,706) is sometimes argued as appropriate because of the lower pain profile of patients with haematological cancer (122,707,708). What these findings reveal, however, is a burden similar if not exceeding the burden reported in general cancer (704), thereby refuting this traditionally held believe (709). When comparing findings of this study with findings from studies including haematological cancer populations referred to SPC services, it becomes apparent that the argument of a different and lower symptom profile applies to some leukemia and lymphoma patients. In acute leukemia, although presenting with a comparable median number of symptoms, patients reported a much lower prevalence of pain (275). This was also found in an outpatient SPC population (710), including lymphoma patients. Pain did not make the list of the five most frequent symptoms. This finding points towards the heterogeneity inherent in the haematological cancer population. Multiple myeloma may show a different pattern of complexity in symptoms, of dependency and functional decline. Overall the pattern is more common to the one seen in non-malignant organ failure conditions. Patients with multiple myeloma may be comparable to certain haematological conditions that similarly affect the elderly (i.e. chronic myeloid leukemia, myelodysplastic syndrome). These differences in the trajectory towards the end of life between haematological conditions are not well understood and most likely add to the barriers regarding palliative care involvement.

Johnsen and co-authors in their study from 2009 (9) concluded that patients with multiple myeloma reported a consistently higher symptom burden and more QOL problems than other haematological cancer patients. Some studies in myeloma that included QOL data also included normative comparisons to general populations or cancer populations (9,22,35,90,485,490,495). To better understand how multiple myeloma patients compare to cancer and non-cancer conditions, data from the EORTC QLQ-C30 were graphed and compared to these groups in Figure 11. In comparison to the general population, scores of global QOL and QOL domain scores reported in this study are consistently lower than in the general population as can be seen in panel (a) in

Figure 11. This relationship also holds for most functioning domains when comparing to general cancer populations. Particularly physical, role and social functioning appear to be the domains the most affected, with the confidence intervals not including the mean functioning scores of normative cancer and non-cancer populations. Comparable or slightly higher levels of overall QOL and emotional functioning to those found in non-malignant conditions are reported. This study also demonstrates significant impairments regarding the symptoms pain, fatigue and sleep problems relative to cancer and non-malignant population data. The severity of dyspnoea again

Figure 11: Norm comparison of QOL and symptom data from this study to the general and cancer population



Abbreviations: AP: appetite loss, CI: confidence interval, CF: cognitive functioning, CO: constipation, DI: diarrhoea, DY: dyspnoea, EF: emotional functioning, FA: fatigue, FI: financial difficulties, NV: nausea/vomiting, PA: pain, PF: physical functioning, QL: overall quality of life, RF: role functioning, SF: social functioning, SL: sleep problems.

Studies providing norm populations: General population in Hjermstad et al. (1998) (711), general Swedish population in Michelson et al. (2000) (712), general Dutch population in van de Poll-Franse et al. (2011) (713), non-malignant long-term disease in van de Poll-Franse et al. (2011) (713), post-SCT patient data in Kopp et al. (2005) (714), general cancer population in Fayers et al. (1998) (715)

exceeds the one found in all cancer and in non-cancer normative comparison data. Overall, the previously observed considerable decrements in QOL and functioning and symptom scores (496) have also been observed in this study.

Contrasting with the results from the symptom prevalence analysis, impairment of cognitive functioning seems to be lower than the prevalence reported based on the MyPOS item "problems remembering". This discrepancy can potentially be explained by the different definitions of cognitive functioning measured in the MyPOS and the EORTC subscale. The QLQ-C30 focuses more on aspects of concentration, whereas the MyPOS asks about subjective problems with recall or memory (384). Both aspects are a legitimate part of cognitive dysfunction but represent different concepts. One qualitative study (482), focusing on perceived cognitive impairment in multiple myeloma reported various problems with memory, recall and lack of concentration contributing to diminished role functioning and interference with personal and professional life. Inconsistencies in definitions and measurement of cognitive phenomena have been shown to affect prevalence and severity estimates (716,717).

Table 8 presents a comparison of results from this study with pooled data from all myeloma studies containing QOL data from the EORTC QLQ-C30, split by disease stage, newly diagnosed, mixed (all types) and advanced disease, and contrasting autologous stem cell transplant samples (ASCT) with the chemotherapy treatment group. ASCT samples present with consistently lower symptom burden (except for short-term side effects of the procedure itself, like diarrhoea). The longest prospective longitudinal study including multiple myeloma ASCT patients tracked symptoms and QOL over three years (31). All patients recovered quickly, as early as the second month after SCT with role and social functioning taking longer to reach baseline levels. This study showed that QOL in this group reached baseline levels early on and remained stable over long time periods. However, a different impact of ASCT has been described by Frick et al. (2004) (30,32) and Hjermstad (2004) (718). The finding of comparably lower burden is interesting as reviews usually conclude that the group of SCT patients is more burdened than those treated with second or third-line chemotherapeutical regimes (719-721). Differences between the ASCT and non-ASCT groups could be explained by differences in measurement time points. QOL could have been measured later in the disease trajectory in stable phases than in the non-ASCT population. Other confounding variables could be age and comorbidity. High-dose therapy with ASCT is considered the front-line treatment and standard care in younger and fitter patients (220). Older patients with comorbid conditions and a poor performance status are not subjected to high-dose therapy with the initial therapy consisting of thalidomide or bortezomib in combination with an alkalyting agent or a steroid (71). However, these therapies produce less durable remissions. QOL has been shown to increase with length of time off chemotherapy (83). This study showed QOL impairment levels more similar to the non-ASCT population. The comparison between

ASCT and non-ASCT groups was not possible in this PhD study since not enough patients were undergoing this procedure during the study period.

Table 8: Comparison of quality of life results from this study with existing studies (EORTC QLQ-C30 instruments)

Symptoms/QOL	This study	Meta-analysis		Subsamples meta-analysis	
	Mean (95% CI)	n	Mean (95% CI)		
Fatigue	41.3 (36.6–46.3)	6197	43.3 (32.7–53.8)		
Newly diagnosed	45.0 (28.2–61.8)	3762	45.9 (26.2–65.6)	ASCT	42.2 (24.3-60.0)
Mixed	–	506	40.5 (20.0–61.0)	Non ASCT	43.9 (30.7-57.0)
Advanced	42.7 (32.6–52.7)	750	40.2 (13.4–66.9)		
Nausea / vomiting	5.1 (2.9–7.4)	2545	8.0 (3.8–12.3)		
Newly diagnosed	5.0 (3.1–13.1)	1239	2.6 (0.5–4.6)	ASCT	7.9 (3.3–12.5)
Mixed	–	506	7.6 (4.9–10.2)	Non ASCT	8.5 (2.6–14.3)
Advanced	8.7 (2.4–14.9)	186	8.5 (1.3–15.8)		
Pain	28.8 (21.1–32.4)	5964	36.0 (26.4–45.6)		
Newly diagnosed	26.7 (10.6–42.8)	3762	45.6 (27.7–63.5)	ASCT	32.5 (16.5–48.5)
Mixed	–	506	32.6 (13.5–51.7)	Non ASCT	37.9 (25.9–49.9)
Advanced	30.7 (21.0–40.3)	750	38.7 (16.0–61.4)		
Breathlessness	26.7 (21.1–32.4)	2479	25.3 (14.3–36.2)		
Newly diagnosed	40.0 (12.9–67.1)	1173	26.1 (11.6–40.7)	ASCT	26.2 (12.0–40.4)
Mixed	–	506	25.6 (3.2–48.0)	Non ASCT	23.8 (6.6–41.0)
Advanced	26.7 (16.9–36.4)	186	23.8 (15.0–32.7)		
Sleep problems	29.3 (22.8–35.8)	2989	31.2 (17.7–44.7)		
Newly diagnosed	20.0 (3.3–36.7)	1173	29.4 (12.7–46.2)	ASCT	28.9 (9.4–48.3)
Mixed	–	506	35.4 (12.4–58.4)	Non ASCT	33.3 (14.7–52.0)
Advanced	25.3 (12.6–38.1)	285	25.0 (17.6–32.4)		
Appetite loss	15.4 (10.2–20.6)	2877	17.6 (9.5–25.8)		
Newly diagnosed	16.7 (4.1–29.2)	1239	12.0 (7.8–16.3)	ASCT	16.7 (7.7–25.7)
Mixed		506	16.0 (5.9–26.0)	Non ASCT	21.6 (2.8–40.4)
Advanced	24.0 (12.4–35.6)	186	20.6 (0.9–40.3)		
Constipation	16.1 (10.2–22.0)	2530	10.5 (4.2–16.7)		
Newly diagnosed	20.0 (5.6–34.4)	1224	18.0 (12.0–24.1)	ASCT	8.5 (1.7–15.2)
Mixed		506	18.9 (1.8–36.0)	Non ASCT	21.8 (5.6–37.9)
Advanced	28.0 (15.0–40.9)	186	14.7 (0.0–29.3)		
Diarrhoea	8.4 (4.9–11.9)	2530	12.5 (7.7–17.4)		
Newly diagnosed	10.0 (6.1–13.9)	1173	7.9 (0.9–14.9)	ASCT	13.0 (7.7–18.3)
Mixed		506	9.0 (5.2–12.7)	Non ASCT	
Advanced	9.3 (3.0–15.6)	186	8.3 (0.5–16.2)		10.3 (1.4–19.3)
General QOL	63.3 (58.9–67.6)	6704	56.7 (47.9–65.6		
Newly diagnosed	53.3 (37.6–69.1)	7845	55.1 (43.4–66.8)	ASCT	53.0 (37.7–68.4)
Mixed		1458	63.5 (51.7–75.3)	Non ASCT	58.6 (47.8–69.4)
Advanced	59.3 (51.3–67.4)	1665	57.6 (42.2–72.9)		

Symptoms/QOL	This study	Meta-analysis		Subsamples meta-analysis	
	Mean (95% CI)	n	Mean (95% CI)		
Physical	67.1 (62.5–71.7)	6042	61.6 (51.9–71.3)		
Newly diagnosed	62.7 (46.6–78.8)	1526	52.2 (23.0–81.3)	ASCT	65.8 (47.2–84.4)
Mixed		718	55.9 (30.8–80.9)	Non ASCT	60.0 (48.6–71.4)
Advanced	64.0 (54.4–73.6)	186	59.4 (18.9–99.8)		
Role	63.6 (57.6–69.5)	3164	53.5 (36.7–68.4)		
Newly diagnosed	60.0 (38.8–81.2)	1526	52.2 (23.0–81.3)	ASCT	49.6 (25.5–73.7)
Mixed		718	55.9 (30.8–80.9)	Non ASCT	55.9 (37.1–74.7)
Advanced	60.7 (49.5–71.9)	186	59.4 (27.9–90.8)		
Emotional	77.4 (72.6–82.1)	3597	69.7 (59.7–79.8)		
Newly diagnosed	73.3 (53.1–93.6)	1526	74.3 (52.6–96.0)	ASCT	71.1 (53.5–88.7)
Mixed		718	75.2 (58.9–91.6)	Non ASCT	69.1 (56.8–81.3)
Advanced	79.7 (70.7–88.7)	619	57.0 (20.1–93.9)		
Cognitive	78.6 (73.9–83.2)	3085	78.4 (67.9–88.9)		
Newly diagnosed	73.3 (57.2–89.4)	1526	77.2 (55.0–99.4)	ASCT	82.5 (65.4–99.7)
Mixed		718	80.4 (64.1–96.7)	Non ASCT	76.1 (62.9–89.2)
Advanced	76.0 (66.9–85.1)	186	76.1 (53.2–99.1)		
Social	67.0 (61.0–73.1)	3318	66.6 (54.2–78.9)		
Newly diagnosed	58.3 (33.0–83.6)	1526	66.6 (44.6–88.5)	ASCT	66.6 (54.2–78.9)
Mixed		718	72.2 (50.4–94.0)	Non ASCT	69.6 (53.6–85.6)
Advanced	64.0 (51.0–76.9)	186	65.4 (30.9–99.9)		
Financial	10.6 (5.4–15.9)	2148	23.7 (14.7–32.7)		
Newly diagnosed	3.3 (0.2 – 6.4)	542	16.5 (0.9–32.0)	ASCT	26.0 (15.3–36.7)
Mixed		506	17.6 (3.9–31.3)	Non ASCT	18.1 (1.5–34.7)
Advanced	10.7 (0.4–20.9)	154	8.8 (6.1–11.5)		
Disease symptoms	24.4 (20.4–28.3)	3698	32.5 (19.1–46.0)		
Newly diagnosed	29.4 (18.5–40.4)	2606	30.8 (5.4–56.2)		
Mixed		319	42.6 (6.9–78.3)		
Advanced	23.1 (16.1–30.1)	619	25.7 (1.2–50.1)		
Side effects	15.4 (12.9–17.9)	3085	26.0 (14.1–37.8)		
Newly diagnosed	18.0 (5.1–30.9)	2147	20.2 (0.7–39.7)		
Mixed		319	38.4 (4.4–72.4)		
Advanced	16.9 (12.4–21.5)	619	19.3 (1.7–36.9)		
Body image	20.9 (15.3–26.4)	745	48.4 (24.2–72.6)		
Newly diagnosed	30.0 (6.3–53.7)	240	80.0 (76.2–83.8)		
Mixed		319	58.3 (21.7–94.8)		
Advanced	16.0 (7.9–24.1)	186	23.4 (15.3–31.6)		
Future perspect.	36.4 (31.1–41.6)	899	49.6 (30.4–68.9)		
Newly diagnosed	37.8 (16.8–58.7)	240	42.3 (38.9–45.7)		
Mixed		319	51.6 (19.5–83.7)		
Advanced	33.8 (25.8–41.8)	186	46.6 (15.1–78.2)		

In the cross-sectional study the three MyPOS subscales (except for the Healthcare support subscale) and the MyPOS total score differed significantly between disease phase. Severity or impairment was highest in the progressive, advanced or relapsed phase, followed by newly

diagnosed patients, with lowest values reported in stable phase. The same pattern was seen in the EORTC subscales global QOL, physical functioning and role functioning. The QLQ-MY20 subscale 'Side effects of treatment' departed from this pattern with post-hoc tests showing the highest amount of side effects in the stable phase, possibly demonstrating the time lag and chronicity of accumulating treatment toxicities. The first regression model also revealed disease phase to be significantly associated with the total MyPOS score. This relationship between disease duration, symptom burden, and treatment side effects was also observed in a smaller, cross-sectional European cohort study (593). All these variables, together with treatment status and bone pain among symptoms were found to be strong predictors of global health status.

However, disease phase does not equal time since diagnosis as was demonstrated in a small Dutch survivorship study in myeloma. Length of survivorship had no impact on the global health subscale of the EORTC QLQ-C30, nor its subscales (381). A study by a UK research group used a similar definition of phase as this PhD study (83), although the authors divided phase into treatment-free intervals and lines of treatment and did not distinguish at all between phases on and off-treatment beyond second-line treatment. The EORTC QLQ-C30 physical, role, emotional and social functioning; the QLQ-MY20 future perspectives; side effects and body image subscales all demonstrated significantly positive associations with the first treatment-free interval (83). Despite these significant relationships, QOL variables did not exhibit large differences between treatment phases and the later stage, which might be an artefact of the grouping that the authors used. A third study supporting the finding of fluctuant QOL per disease phase was conducted by Boland and coauthors (2013) (593) involving advanced, but stable patients. The authors defined this phase as being in a later treatment-free interval after a prior median of three lines of treatment. A median of 5.5 years from diagnosis markedly compromised physical functioning was found together with fatigue and pain as the dominating symptom that significantly differed to early disease (593). Later disease stage was also characterised by greater symptom burden, reduced body image and greater impairment in future perspectives. A possible explanation is that especially in later relapses, many patients will have accumulated complications or side effects of previous treatment regimens that will impair QOL (68).

The finding of more advanced disease being associated with poorer HRQOL scores has not been unequivocally reported in the haematological cancer literature. The relationship holds true for non-Hodgkin lymphoma patients (722,723), but in Hodgkin lymphoma the reverse finding of relapsed patients not reporting worse HRQOL than those remaining disease-free has also been reported (722,723). In mixed haematological cancer samples, usually more advanced disease stage, coupled with being on-treatment and having a poorer performance status, are accompanied by poorer HRQOL functioning scores (93,724). Our finding of a high symptom burden in patients newly diagnosed with myeloma (which, according to our definition, entails patients waiting for

treatment to begin, being on treatment or receiving maintenance treatment after first-line treatment) is also new. It demonstrates that palliative care cannot focus on the later stages of disease alone but makes the early integration of palliative care and supportive care for a variety of problems and unmet needs important. A network meta-analysis of baseline QOL data from six bortezomib randomised controlled trials in myeloma published this year reported similar mean EORTC global health scores across newly diagnosed, early and late disease phases (725). Unexpectedly, functioning subscales were higher in the later stages, indicating a better perceived health status. In addition, symptom scores, including pain, were similar or lower in the later versus earlier stages. Similarly to our study, this suggests a better symptom control with more advanced disease. Also, newly diagnosed patients tended to have more fatigue and greater loss of appetite, a result that was also found in this PhD study, with higher fatigue severity, breathlessness, disease symptoms and more problems with future perspectives reported at baseline. Other possible explanations for this finding could be adaptation and response shift processes (299,726-728), influencing the perception of burden and impact on QOL. A possible sample bias could be present in Robinson et al.'s (2006) (725) study due to pooling data from bortezomib studies and including baseline data from clinical trials only. These inconsistent results point towards the difficulty of basing need on a survival/prognosis model. A high symptom burden and amount of QOL impairment can be present from the beginning of disease and needs to be addressed. These findings also point towards different trajectories over time and a potentially heterogeneous population of myeloma sufferers. To understand this heterogeneity and risk of deterioration, following individuals over time as they progress through different phases of disease is needed.

Longitudinal evidence to date is mainly derived from clinical trials, which either only include newly diagnosed but transplant-ineligible patients (365,366,370-373) or relapsed/refractory patients (23,375-377,729). From this data, no typical trajectory of QOL can be determined, as patients represent a selected group, and low compliance and possible selection bias regarding age and comorbidity are likely to occur (147,148,730). The second group of studies providing information on the course of symptoms and QOL over time include those in ASCT samples. Sherman et al. (2009) (35) compared data from stem cell collection with post-transplantation QOL and reported patients recovering with less pain and fatigue, but worsening levels of anxiety, depression and general well-being. Pillay et al. (2015) (731) compared the course of psychological symptoms 2-3 weeks post transplantation to 3 months post-SCT, at which point the proportion of anxiety and depression and general QOL scores dropped below the baseline level. Four studies focused on experiences during ASCT and followed the course of symptoms over this usually 28-day long period (29,378,690,731-734). They all reported the highest prevalence of symptoms at point of nadir with subsequent recovery of levels. This PhD study is the only study

presenting symptom prevalence over an eight months period in multiple myeloma. Overall, the general decrease in symptom prevalence reported in the studies above was also observed in this study. However, baseline levels well exceeded levels reported in SCT studies. For example, pain (67.6%), breathlessness (56.7%) and fatigue (83.6%) were considerably higher at baseline than in the SCT population, with the exception of the prevalence of fatigue in Sherman et al.'s (2009) (35) study. At 8 months, these rates reduced to 42.4% for pain, 39.1% breathlessness and 52.5% for fatigue. The last comparable time point to SCT studies was at 2-3 months post-baseline. Sherman (35) reported a prevalence of 30.9% for pain. Anderson and co-authors (2007, 2011) (29,734) reported a prevalence of 8% for breathlessness. Similarly to the elevated levels of psychological symptoms and their rise over time described in reviews and studies of symptom burden in haematology/SCT populations (35,719,735,736), we observed a rising prevalence for anxiety and depression. Psychological distress has been shown to be associated with a high or very high level of unmet supportive care needs in haematology and myeloma (90,526). Thus, the sample in this study seems to experience a decrease in symptom burden but not as pronounced as those reported in SCT samples. However, psychological distress becomes a much greater issue over time. It should be borne in mind that the comparison to SCT samples is a comparison to a mixed cancer population, containing a maximum of 30% patients with multiple myeloma. This sample, however, contained a mixture of myeloma only patients at different points in their disease trajectory, some of which were several years post-SCT. This leads to a symptom profile that is characterised by a blend of disease-related and short- and long-term toxicities of treatment, including organ dysfunction, comorbid disease and other complications.

In palliative care, knowing the pattern of illness in terms of understanding the trajectories of functioning, symptoms and concerns informs patient-centred care and underpins service provision at the end of life (565,737). High levels of symptoms and other problems show areas that need to be addressed and help focus care on needs, thereby shifting from a diagnosis-oriented/treatment-oriented focus of slowing the progression of disease towards a more patient-centred model of care that includes much greater recognition of the extent to which symptoms and concerns impact on patients' QOL. Recognising drivers of psychosocial, practical and social consequences of some of these symptoms and their impact on functioning would promote assessment and intervention beyond disease-orientated and pharmacological interventions in multiple myeloma, including more and appropriate psychosocial assessment and support. For multiple myeloma, this information is largely missing, with the main evidence on HRQOL stemming from clinical trial evaluations (738). Large observational cohort studies that investigate changes in patient-reported outcomes over the disease course, thereby spanning multiple therapeutic interventions and trajectories (725), are missing. In this study, we tried to partly fill this gap by following a naturalistic, prospective multi-centre group of patients as they progressed from diagnosis and

initial therapy to later stages (359). Ideally, follow-up should be long enough the see the progression across the whole disease and treatment course, from diagnosis to advanced disease, capturing multiple therapies, treatment-free intervals and the use of supportive care services.

Population trajectories have implications for the provision of care to a population as a whole. They might indicate areas of greater need where resources should be focused, also showing areas for proactive targeting of intervention to alleviate symptoms early. Some of this work has been conducted in multiple myeloma regarding the beneficial role of early exercise interventions to address fatigue (488,739,740). However, mean trajectories can obscure subgroups of QOL impairments and persisting symptoms. Individual trajectories have implications for care provision for the individual patient. Therefore, the aim of this study was to understand the considerable heterogeneity in QOL and functioning trajectories in this large sample of MM patients. When graphing the mean QOL trajectory for the whole group and overlaying this picture with the individual trajectories, it became apparent that analysing the mean trajectory would mask important between-subject variation and probably lead to wrong conclusions regarding influencing factors.

Therefore, an approach combining the multivariate, longitudinal analysis of trajectories with cluster analysis was used to understand the heterogeneity and to split the sample into groups or classes of common QOL experience. Groups of QOL experience seemed to follow a stable course, either characterised by a high or a low level of QOL throughout the trajectory (class 2, stable, good QOL and class 3, stable poor QOL). A rising/declining trajectory of improving QOL (class 1) and deteriorating QOL (class 4) was found in addition. Progressive decline was confined to a few patients only, the class of poor but stable QOL experience was larger (n = 24). Trajectories of fluctuant decline were not identified in this research. Other than in the cross-sectional analysis in which duration of illness or disease phase influenced poor QOL, these results highlight that there is a group of patients that consistently are more poorly or show a rapidly declining trajectory. A comparison to other longitudinal studies is hindered by the fact that the only other observational longitudinal study in myeloma (381) only included two time points, one year apart, and only described mean change in QOL and its domains, not exploring heterogeneity within the sample.

Analogous to a seminal study by Murray et al. (2002) (737), we wanted to better understand how the overall trajectory of QOL in these classes related to aspects of QOL functioning and thus graphed physical, role, emotional and social functioning as well as side effects of treatment for each class (see chapter 6). For the classes improving QOL, stable good QOL and deteriorating QOL the trajectory of QOL seemed to be largely determined by the level of physical functioning, with social functioning and role functioning following this course as well. Only the class of stable,

poor QOL showed a remarkably fluctuant course of QOL domains with all functioning aspects first showing improvement and then returning to baseline levels around four to six months. This points towards domain scores possibly indicating overall risk of deterioration in QOL, a fact that was explored in the regression analyses.

8.1.2 Risk factors for poor and deteriorating HRQOL in multiple myeloma

After identifying the group of myeloma patients with a poor QOL, the last step in the modelling consisted of considering risk factors for experiencing poor or deteriorating QOL. A two-step procedure was followed. Firstly, a model of independently associated factors was built from the large, multi-centre cross-sectional dataset using the MyPOS, EORTC global QOL scale, and EQ-5D Index (UK norm) as dependent variables. The rationale for including different dependent variables in this step was to follow a wide definition of poor quality of life and integrating results from the meta-analyses (see chapter 2.2.2.3). The three measures represented different methods of capturing QOL, one being a global rating, one a generic utility measure and the MyPOS being a multidimensional questionnaire with a focus on palliative care aspects in multiple myeloma. Consistency of independent factors between the models was proposed as a method of internal validation (613,624). Models were built using Altman's recommendations (741) for prioritising variables. First univariate linear regression models tested each of the symptoms. Bivariate analyses were conducted to determine the socio-demographic, disease and treatment history variables to enter into the model. Those symptoms found significant were combined in a multivariate model which was then trimmed to exclude those that lost significance. The second step consisted of hierarchical regression procedures, adjusting for general symptom level and entering variables step-wise into the model. For the longitudinal study, the risk model was built differently by using not a QOL outcome per se as the independent variables, but focusing on the combined classes of those patients with stable poor QOL and deteriorating QOL found in the trajectory analysis. Instead of validating the model from the cross-sectional analysis by using the same significant predictor variables and testing their magnitude, the model was validated by essentially building a new exploratory model and comparing the predictors to the cross-sectional analysis. This was necessary because of the change in outcome (class membership and no linear dependent variable). Again, bivariate associations were tested first and those variables found to be significant entered into a multivariable logistic regression.

The regression model in the cross-sectional analysis showed a mediating influence of general symptom level only for the outcome palliative care concerns/total MyPOS. Symptoms predicted all three outcomes, but of the ones entered only pain showed consistent associations with all three outcomes. Fatigue was found to be a significant predictor variable in the EORTC QLQ-C30

global QOL model; dry mouth/mouth problems was associated with higher palliative care concerns. Psychological symptoms exhibited a consistent relationship with all outcome variables. ECOG performance status of 3 or higher was independently associated with the EQ-5D index score. The amount of variance explained in the models was lowest in the model of global QOL (51.4%) and highest in the model of palliative care concerns (MyPOS) (88%). All socio-demographic variables, disease and treatment characteristics (age, gender, ethnicity, educational level (as an indicator of socio-economic status), working status, type of myeloma, ISS stage, comorbidity, lines of treatment, treatment intensity) needed to be removed from the model due to non-significance. Once entered into the multivariate models, the explanatory power of symptom and functioning variables let these variables drop from the model. At the bivariate level in the cross-sectional analysis, age, being on treatment, working status and type of myeloma (light chain disease versus IgA or IgG myeloma) were found significant. Of these, only stage of disease and age remained in the multivariate model. In the longitudinal regression model, only phase of illness remained significant in the final model. Overall, results from the longitudinal study confirmed the results from the initial exploratory analysis. However, it should be noted that there is a common element between the two parts of the study since baseline data from the longitudinal survey was included in the secondary analysis. Overall, although the outcome variable was changed between the two models, common variables working as risk factors for poor or deteriorating QOL emerged: general symptom level, presence of pain and fatigue (and possibly mucositis), performance status and psychological/mental health status. Interestingly, when defining classes of QOL trajectories the influence of phase of illness was obliterated, meaning that poor or deteriorating QOL was not bound to a specific disease phase. This also highlights the fact that poor or deteriorating QOL can be present in newly diagnosed patients, a result found in the descriptive analysis. Support for this view comes from studies with radiation or chemotherapy patients in which fatigue was present even before the begin of treatment and persisting at even higher than baseline rates for years (34,35,742). It also means that identifying patients that need palliative care involvement cannot rely on factors such as disease phase or functional status (as was the case in the initial proposal by Lynn and Lunney (157)) alone.

Support for the role of symptoms in predicting poor QOL and at-risk groups comes from a large population-based study of mixed cancer patients, among them 120 myeloma patients (743). Multivariate modelling revealed fatigue to be correlated with poor performance status, having active disease and feeling sad and irritable (743). Particularly the role of pain cannot be overstated. It has consistently been shown to be a strong determinant for QOL, particularly in myeloma (744). Recent Italian studies (501) into the nature of pain experienced by haematological cancer patients illustrate that sources of pain are manifold, with pain mechanisms not only involving bone pain or neuropathic pain, but even incident pain being aetiologic for 38%

of all pain syndromes. Bone lesions and bone involvement cause the majority of pain syndromes (501). They can increase bone resorption, leading to skeletal complications (pathologic fractures, spinal cord compression, hypercalcaemia and severe bone pain), and thus may substantially reduce functional independence and QOL. They have been shown to be related to survival in multiple myeloma and other diseases (745-747). Mucositis has been identified as a critical risk factor for infections and is a major driver of analgesic and total parenteral nutrition use (91,496,502), also increasing nutritional risk, a factor identified as a major driver of QOL in the meta-analysis of predictors of QOL (see chapter 2.2.2.3).

The strong interrelationships in this study have also been established in other studies, particularly between overall QOL, greater symptom burden and poorer outcomes (483,748,749). Symptoms appear in clusters, of which the two most common are: pain – fatigue – physical functioning (90,365,750-752) and pain – fatigue – depression (598). It has been hypothesised that particularly pain and fatigue can have a common underlying cause (744,753,754), since adequate pain control has been shown to reduce fatigue (365). Similar interrelationships are reported in the wider cancer literature in prospective studies of oncological patients with advanced cancer (755). Hwang et al. (2003) (756) demonstrated correlations between fatigue, dyspnoea, pain, lack of appetite, depression and irritability. Positive correlations of fatigue with performance status and negative correlations with depression and haemoglobin levels were described in elderly cancer (757) and haemato-oncological patients (758). Fatigue and pain seem to have high correlations throughout the disease course in multiple myeloma (381,752). This can be partly explained by the chronicity of this condition with frequent relapses after remission or partial remission, leading to an accumulation of disease- and treatment-related problems.

Symptoms have a considerable impact on aspects of QOL. In a study of 379 patients receiving chemotherapy, almost all fatigued patients said symptoms prevented a normal life and changed their daily routine (759). The presence of symptoms influenced physical functioning and physical activity in particular (760-763), decreased functional ability leading to lower QOL (764,765) and negative effects on mood and psychological health in as little as seven days (766). The role of performance status has recently been demonstrated in a network meta-analysis of six bortezomib trials in multiple myeloma, with performance status persistently influencing global health status across all disease stages (725). Poor physical function can result in increased dependence, restricting family life and role functioning (743,767). However, performance status and physical functioning cannot explain differences in QOL alone. As seen in the regression analysis, symptom variables and psychological distress showed higher beta coefficients than performance status or physical functioning. There is a role for performance status to be used as a stratification variable to indicate the need for screening of general symptom level, symptom burden and mental health. Previous research suggested that physical activity may be an important intervention in the group

of multiple myeloma to decrease overall symptom and fatigue levels (739,768-770). Expanding supportive care interventions to include exercise seems warranted since a population-based study showed that all physical activity levels declined from pre-diagnosis levels soon after diagnosis and completion of first-line treatment with long-term consequences for physical functioning later in the disease trajectory (771).

In this study, clinically relevant anxiety and/or depression at baseline emerged as an important predictor for poor QOL. This is relevant since only one quarter of all participants presented with clinically relevant psychological distress. Psychological distress, coupled with the symptoms pain and fatigue and functioning therefore represents an important screening and assessment variable to indicate possible palliative care needs. Higher anxiety and depression in general have been linked to higher supportive care needs in the literature (529,772). Rates of anxiety and depression are particularly high among individuals with multiple myeloma (90), in part higher than in the wider cancer literature (773,774). It has been proposed that pain, fatigue and depression/anxiety form a symptom cluster, but no strong evidence for a cause and effect relationship has been provided to date (775). Pain is associated with anxiety/depression, when comparing cancer patients with pain to those without (776,777). Ahles and co-authors (1983) (776,777) found pain to be related to pain-specific anxious mood and global distress. Pain and its treatment may cause fatigue directly or indirectly through stress responses. In multiple myeloma and other haematological disease, strong associations between depression and high levels of fatigue and, to a lesser extent, between anxiety, fatigue and comorbidity have been reported (778). This relationship also holds true in studies of bone marrow transplantation patients (779). Associations may be due to mood disturbances resulting from the psychological impact of cancer and/or the neurotoxic effects of cancer (780). Since not all participants in this study experienced this triad of symptoms, it is likely that such a symptom cluster is not universally present but that the link of these symptoms indicates a higher impact on QOL in general, possibly by symptoms influencing functioning and mood factors leading to inefficient coping or making the individual more susceptible to the debilitating influence of these symptoms on well-being. Some authors argue that the high correlations between these measures represent an artefact and highlight problems with discriminant validity because of the considerable overlap between these entities (339,340,356,781,782). What was not possible in this analysis was the investigation of whether psychological factors function as stable predictors or whether they are responsive to treatment (see section 8.5.1). The regression analyses highlight the need to treat these symptoms since they can compromise the timing or completion of treatment regimes, either as dose-limiting adverse effects or because they reduce patients' compliance and willingness to adhere to treatment (783). The failure to complete the optimal schedule reduces the chance of remission and length of remission (86,784).

One drawback of the predictive model built to indicate risk of deterioration or poor QOL in multiple myeloma is the lack of biomedical variables that could be taken into account. One of the candidates for investigation is anaemia. In multiple myeloma patients, anaemia is present in about half of myeloma patients at diagnosis (205) and in most patients during the course of disease, either caused by cancer or its treatment, which can induce fatigue (161). Haemoglobin concentrations are associated with the type of tumour, the extent of disease, response to treatment and relapse, all of which can have an impact on QOL and suggesting an independent relationship of haemoglobin and QOL. However, this relationship remains uncertain and recent studies in myeloproliferative disorders and in myeloma patients have shown that oftentimes, haemoglobin levels provided little insight into levels of QOL (161,785-788). For example, the change in mean QOL scores was modest in trials of epoetin alpha (185,494,789-791). Fatigue levels often indicated larger changes in the global QOL EORTC QLQ-C30 scale, as large as four times the magnitude of a clinically meaningful difference, when compared to anaemia as an explanatory variable (767). Elucidating the role of anaemia as a predictor might have important implications since the haemoglobin level at disease onset is an important factor on which treatment decisions are based. However, patient-reported outcomes rather than the degree of anaemia may more accurately reveal the effects of disease burden on QOL functioning. Similarly, monitoring of cytokines has been proposed, among them interleukin (IL)-1, tumour necrosis factor (TNF)-alpha and various other (792,793). Cytokines like IL-6 have been related to disease activity in multiple myeloma (188). IL-6 has been shown to correlate with pain, physical functioning, sleep problems, and appetite loss in advanced disease (593,794). Wang and co-authors (2015) (379), in a recent longitudinal study of myeloma SCT patients, demonstrated that elevated baseline levels of TNF-a predicted membership in the high-symptom group. They found cytokines to be related to the severity of symptoms, whereas treatment-related factors such as maintenance therapy and tumour response were not related (190). This is contrary to a study that reported a relation between cytokines and a poor response to chemotherapy, therefore suggesting IL-6 and others markers as screening measures that could identify a subset of patients with a high risk of treatment failure (783). Other biomedical factors linked to QOL and survival are albumin and creatinine clearance rate, mainly due to their relationship to renal involvement which can be a factor affecting survival in myeloma (725). However, since these variables are confounded with disease complications like osteolytic lesions, their appropriateness for screening has been described as limited (183). The same is true for C-reactive protein (CRP) values that may be confounded with haematological disease factors and a chronic non-infectious inflammation process (183).

In general, although some studies in myeloma demonstrated a relationship between baseline values and symptoms/QOL, correlation coefficients were generally of low to moderate strength. The meta-analysis of factors being associated with QOL presented in chapter 2.2.2.3 synthesised

these studies and came to a similar conclusion. Much of the evidence also focuses on early disease stages with the predictive power of these variables needing to be established in later stages. A major critique of biomarkers has been around their lack of adequate sensitivity and specificity, concluding that they are not suitable as predictive factors for survival, disease progression, response to treatment and QOL in particular (191). Thus, although counterintuitive at first, biomedical factors may show lower predictive power than symptoms and individual psychological factors (795), a finding that has been observed in both regression analyses. However, future studies should focus on the link between traditionally proposed targets for monitoring, like disease progression and response to treatment, and QOL.

One surprising finding was that comorbidity did not reveal any sizable influence on HRQOL. Comorbidity in particular has been suggested as one of the main factors driving mortality in MM and has been included in recent models of prognosis in palliative care. For multiple myeloma, a number of comorbidity indices have been tested (95,206-209,702). The Charlson comorbidity index, assessing 19 comorbid conditions, is the one most frequently used. Other indices are the Freiburg comorbidity index, including patients' Karnofsky performance and renal and lung disease status (206). Comorbidity has been linked to mortality in myeloma (796), particularly in the presence of renal disease, dementia or cardiovascular and pulmonary disease and most likely due to patients receiving less-intensive treatments. Comorbidities associated with organ failure or cognitive function are associated with poorer prognosis (199,214,797-800), especially among patients in HSCT transplant population (702,801,802). Patients with a high number of comorbidities more often report lower levels of health-related quality of life (803), a result that was not observed in this study. This is striking as these differences between patients with comorbidity and those without have been reported as profound, at least twice the magnitude of the minimal important difference in general health, pain and physical functioning (804). Vissers et al. (2013) (805) reported that comorbidity explained up to 20% of the variance in pain and fatigue, with comorbidity explaining more variation than sociodemographic and cancer characteristics. However, again patient-reported variables like psychological status might exert a stronger link to deteriorating and poor QOL.

The findings of this study generally point towards the need for basing risk stratification in myeloma not only on disease or treatment characteristics. To date, prognostic risk stratification in myeloma is solely based on disease characteristics assessed at diagnosis, ISS or chromosomal abnormalities (806). Linking these prognostic indices to HRQOL has been challenging (245,807-809). Some initiatives in myelodysplastic syndromes produced risk scores composed of traditional biomedical indices and symptom scores (presence of fatigue) (810). Chow and colleagues developed and validated a predictive model for survival in advanced cancer patients including disease variables and Karnofsky performance status, symptom severity and QOL variables (146).

An integration of these variables to potentially indicate need for supportive/palliative care should be validated in later disease stages. Some recent models in palliative care tried to emulate these findings and developed frailty scores that contain patient-reported outcomes (dyspnoea, anorexia), performance status and white blood cell abnormalities (183). The Palliative Prognostic Index (146,811), the Palliative Prognostic Score (204) and the Palliative Performance Scale (203,217,812) all contain symptom information. However, their applicability to the haematological discipline remains to be tested since these tools were designed to indicate short-term mortality of one month. Multiple myeloma is characterised by a long disease trajectory. Another proposal is to recognise frailty as an important predictive factor in multiple myeloma, integrating dependency, comorbidities, disease-specific variables and patient-reported outcomes into a frailty score (95, 694). The data from this study provides an argument for incorporating patient-reported outcomes in these scores. Particularly symptoms and psychological factors were identified as important screening and monitoring variables. These variables, together with physical functioning, have been linked to mortality in multiple myeloma (22,23,242,813). Hypothesising a mediating mechanism by controlling physical symptoms, thus reducing depression and increasing social support and influencing treatment decision making has been proposed in Temel and co-authors seminal study as the reason for why the early integration of palliative care was associated with a survival advantage in this advanced cancer cohort (172,277). This is another argument for including HRQOL and symptom status variables into risk scores. In the next section, I will therefore focus on the assessment of these variables using the Myeloma Patient Outcome Scale.

8.1.3 Longitudinal validity and reliability of the MyPOS

The Myeloma Patient Outcome Scale was developed after an initial systematic review revealed that existing questionnaires in the field were either developed solely or primarily for research purposes and were not covering all the issues important to myeloma patients (359). However, the issue of developing a new questionnaire in light of the abundance of HRQOL tools, generic and some disease-specific, that are already available in haematology and multiple myeloma needs to be argued carefully. One approach recognising the wealth of development and field-test work was to modify an existing questionnaire rather than design a new tool. Therefore, the most successful items from existing questionnaires such as the Palliative Care Outcome Scale (POS) and the EORTC QLQ-MY20 were picked and subjected to cognitive testing involving a large sample of patients with different disease stages (384). This was supplemented with extensive qualitative interviews and focus groups to understand how individuals with myeloma define QOL and what symptoms and problems impact on QOL (357).

Table 9: Comparison of the content and domain coverage of the main myeloma-specific quality of life and symptom questionnaires

QOL domain	Myeloma Patient Outcome Scale (384)	EORTC QLQ-MY20 (221,310)	M. D. Anderson Symptom Inventory – Multiple myeloma (690)
Open questions	✓	–	–
Disease-related symptoms Treatment-related symptoms/side effects	Pain	Pain	Pain
	Breathlessness	Breathlessness	Breathlessness
	Fatigue/Weakness	Fatigue	Fatigue
	Nausea	Nausea	Nausea
	Vomiting	Vomiting	Vomiting
	Poor appetite	Lack of appetite	Lack of appetite
	Constipation	Constipation	Constipation
	Sore/dry mouth	Dry mouth	Dry mouth, Sore mouth
	Drowsiness	Drowsiness	Drowsiness
	Diarrhoea	Diarrhoea	Diarrhoea
	Tingling	Tingling	Numbness or tingling
	Remembering	Remembering	Remembering
	–	Trouble sleeping	Disturbed sleep
	–	–	Muscle weakness
	–	–	Rash
	–	Concentrating	Paying attention
	–	Bone aches	Bone aches
	–	Thirst	–
	–	Restlessness	–
	–	Indigestion	–
	–	Burning eyes	–
Independence/ physical function	Poor mobility	Daily activities Walking	General activity Walking
Emotional well-being and cognitive function	Anxiety Depression Worry about infections	Emotional subscale	Distress Feeling sad Mood
Social/ participatory function	Quality time with friends/family	Social activities	–
Spiritual concerns	Feeling at peace	–	–
Family life/ relationships with others	Family anxiety Sharing feelings	Family life	Relationships with other people
Libido/ sexual function	Worry about sex life	–	–
Role function/Work life	Usual activities	–	Work
Financial concerns	Worry about financial situation	Financial difficulties	–
Leisure activities	Hobbies/Leisure	Hobbies/Leisure	Enjoyment of life
Body image	Physical appearance	Body image	
Quality of health care	Knowledge/skills Care and respect	–	–
Information about disease and treatment	Information as wanted Advice as needed Practical concerns	–	–
Support/ coping mechanisms	Coping with illness	–	–
Thinking about the future	Worry about illness worsening Information about future	Thinking about illness Worry about dying/health	–

Three specific features of the MyPOS are highlighted below, (a) its high content validity, (b) the issue of scaling impact/evaluation instead of severity/intensity, and (c) the use of open questions within a standardised assessment instrument. Table 9 compares the content and domain coverage of the three main myeloma-specific questionnaires, the MyPOS (384), the EORTC QLQ-MY20 (221,310) and the M.D. Anderson Symptom Inventory – Multiple myeloma (690), a tool that was developed post 2012 and was therefore not included in the systematic review of measures (359). Use of qualitative interviews with all stakeholders, but patients in particular, was recently advocated by both the FDA (636) and within the COSMIN guidelines for measure development (640). The MyPOS was built entirely from patient interviews, with clinicians not being involved in the item development or item selection. It is the only measure of three to have done so. When comparing coverage of symptoms among the three measures it is apparent that the MyPOS has the shortest list of items. Despite its brevity, these symptoms were identified by participants in our qualitative study as the most important ones. They correspond to a core set of symptoms that have been considered in other studies as well. The National Cancer Institute proposed a similar list for inclusion in clinical trials as the minimum set of symptoms (814). More importantly, since the MyPOS was also developed with the intention to cover issues important to patients with more advanced disease, the list of included items covers those that are named in studies of commonly held concerns among palliative care patients (259,574,815-817). In fact, these 12 symptoms are covered by the most common QOL and symptom assessment tools but not all contain peripheral neuropathy and memory problems that are included in the MyPOS as important toxicities of treatment (404). Moreover, unlike the MDASI-MM and the EORTC-QLQ-MY20, the MyPOS contains more items regarding worry about the future, information needs, coping processes but also adaptation processes that the prolonged disease trajectory of myeloma asks of individuals. These issues have been also highlighted as important in recent qualitative studies focusing on the advanced myeloma population (385,480,482). Particularly in the studies of Steinhauser and Singer (259,815-817), symptom control was given consistently the highest priority.

This might be related to the fact that the MyPOS, as a QOL tool suitable for use in clinical practice, was designed to probe beyond a simple assessment of symptom status (intensity or severity of a symptom) and instead asks for an evaluation of symptom impact. Therefore, the MyPOS is a QOL instrument and not a health status assessment, the latter being a construct that does not capture all aspects of QOL (295,314,315). A few definitions of QOL particularly highlight this aspect of evaluation, among them the definitions by Calman, Campbell et al. and Frisch (295). These all explicitly refer to internal standards affecting such evaluations. Ferrans (2005, 2007) (295,518), who developed the distinction between health status and health evaluation/impact measures, defines QOL as the satisfaction with those aspects of life that are important to the individual. Asking a patient's evaluation of components of each domain of QOL

requires additional cognitive processing and has the potential of becoming taxing for individuals with cognitive impairment (518). However, evaluating the impact rather than severity has been one of the defining features of the POS, the measure upon which the MyPOS was built and of which it is now a module. The symptom items on the POS are preceded by the statement "Please indicate how much you were affected over the past three days by the following symptoms" (512). The original scale then specified effects on functioning and/or concentration as qualifiers to further probe impact. The issue of scaling impact versus severity is partly related to the QOL model/theory employed. This might also be one argument against Fayers' theory (339,340,356) of distinguishing between QOL items and symptom items in the evaluation of HRQOL measures. He sees symptoms as causal indicators, sufficient to cause a change in QOL. Aspects like anxiety and depression are seen as effect indicators, reflecting the level of QOL. While his theory has a sound basis, evidence from our qualitative study points towards a less stringent relationship between symptoms and QOL. We found that the inter-relationship between symptoms and QOL sometimes matched Fayers' description, but that it could also be mediated by his so-called effect indicators (357). In the initial factor analysis of the MyPOS (384), the functioning items loaded with the symptom items, also pointing towards a different relationship of QOL and symptoms.

The MyPOS has been revised since, on the basis of cognitive interviews with palliative care patients that contested the double-barrelled nature of the scale (818). In the revised version of the POS, the Integrated Palliative Care Outcome Scale (IPOS) (819), the scale was changed to only contain the preceding statement followed by a scale of severity. In keeping with the format of the IPOS, we adapted the MyPOS accordingly. The resulting changes in the endorsement of items, problems with scaling seen in the Rasch analysis and in the assignment of items to scales in the exploratory and confirmatory factor analyses point towards this being an issue of contestation with possible further revisions being necessary.

Recently, there has been a move towards increased development of needs measures arguing that this type of questionnaire is better suited for use in clinical practice to help the clinician recognise the problems experienced by the patient that require help (820). Work to convert the EORTC QLQ-C30 into a needs measures, using the item of fatigue as an example found a high correlation between fatigue intensity and fatigue burden ($r = 0.91$) (820), pulling the distinction between health status and health evaluation into question. However, needs questionnaires often contain a list of items and domains and ask the patient to indicate how much help they want with a particular issue or ask them to rank needs in their importance (521). This approach looses the dimensionality with which domains should be covered in QOL questionnaires. It also requires a full set of possible unmet needs. An issue of greater concern is the narrowness inherent in the concept of need. According to Bradshaw's (1972) definition (532), a need is the possibility to benefit from healthcare. This narrows a questionnaire to probing only those needs that can be

potentially met by an intervention. As indicated in multiple studies (821,822), this can result in important aspects not being included in the questionnaire, like items about sexual concerns, satisfaction with healthcare and family/caregiver burden.

The third strength of the MyPOS lies in its semi-individualised nature. Open questions at its beginning and below the symptom list invite identification of the most important problem(s) and additional symptoms. This allows adding those symptoms not covered by the core set of symptoms, yet keeping the questionnaire reasonably short. In comparison, the MyPOS contains the shortest list of symptoms with less items being devoted to symptoms than in the EORTC QLQ-MY20 and the MDASI-MM (see Table 9). Using qualitative methods to complement standardised questions has been advocated as a way to better capture the totality of the patient's experience (823). This approach partially circumvents the problem of individualised measures regarding difficulties in administration and scoring and the strain this can put on individuals experiencing a high disease and symptom burden (316). In a postal survey of cancer patients from three UK Cancer registries, open questions were completed by 32% (824). We found an even higher percentage of 56% across all five time points in our study. One of the issues and additional symptoms named the most frequently was sleep problems. The issue of sleep disruption and disorders is well-known in haematological and SCT patients (825). One could consider possibly adding this symptom to the core set of symptoms in the MyPOS.

How a change in the wording of the scale and thereby altering the dimensions that are assessed can affect factor analytical results became apparent in the longitudinal psychometric analysis of the MyPOS. Whereas in the initial factor analysis symptoms loaded with functioning items onto one subscale (384), after reformatting the questionnaire and making it a module of the POS, the subsequent change in the scaling of the symptom items also changed the loading of items onto subscales. This underscores the difference between severity and evaluative scaling (518). Although the Rasch model fitted the data well, there were areas of potential improvements (see Table 10). Three out of 33 items did not fit the Rasch model, the three being item 12, Tingling in the hands and feet, item 24, Worry about sex life, and item 33, "Do you have enough information about the future?". Although these three items show fit residuals within the agreed optimum of +/- 2.5 (668), they most likely misfitted due to a high amount of missing data (item 24, worry about sex life, in particular had a high proportion of participants not answering this item). On a theoretical basis, they should stay in the MyPOS because they have been shown to be important areas of concern in myeloma, as is the case with the items about peripheral neuropathy and worry about the future/information needs that have been identified as causing a high proportion of unmet needs in this population (90).

Table 10: Summary of hypotheses and results of longitudinal validity of the MyPOS

Hypotheses/ Domain	Empirical support	Commentary
Objective a) Construct validity		
Structural validity		
A1) Confirming the three-factor structure of the MyPOS	+	Three-factor structure confirmed. Functioning items now loading onto Emotional Response subscale. Fit indices show satisfactory model fit.
A2) After confirmation of subscale structure, evaluation of fit to the Rasch model for each subscale.	+	Fit to the Rasch model for all three subscales (RMSEA < 0.2).
Scaling assumptions		
A3) Determining the individual item fit for each subscale of the MyPOS to identify misfitting and redundant items.	+/–	Overall 30/33 items marginal – good fit Misfitting items according to graphical fit: - (12) Tingling in hands/feet - (24) Worry about sex life - (33) Information about the future Redundant items: - Nausea – Vomiting - Feeling at peace – Depression - Sharing feelings – Family anxiety - Hobbies – Usual activities - Worry illness worsening – Anxiety - Contacting doctors – Knowledge of staff - Contacting doctors – Doctors showing respect
A4) Determining floor and ceiling effects of individual items and subscales	+/–	9/33 items problematic Emotional response subscale and Healthcare support subscale show floor effects (not enough subjects in the sample to cover worse emotional problems or dissatisfaction with healthcare).
A5) Determining validity of response options/scaling	–	21/33 disordered thresholds 10 items: Problems to distinguish between a moderate, severe and overwhelming problem 11 items: Problems discriminating between 'not at all' and 'slight'.
Objective b) Reliability		
B1) Determining internal consistency reliability from factor and Rasch analyses.	+/–	Person separation index (correction for Cronbach' alpha in Rasch analysis): - Symptoms subscale 0.80 - good - Emotional response 0.83 - good - Healthcare support 0.13 - poor Cronbach's $\alpha \geq 0.79$
B2) Determining test-retest reliability and its subcomponents via Generalizability coefficients.	+ +/–	Reliability of screening: R 0.55 to 0.73 - good Reliability of discrimination: $R < 0.50$ - poor Test-retest reliability: $R > 0.90$ - excellent Individual change: R 0.42 to 0.68 - moderate
B3) Determining item invariance over time via differential item functioning analysis in Rasch model.	+	Unstable items over time: - Constipation - Drowsiness - Diarrhoea - Worry about infections

Objective c) Responsiveness		
C1) Determining the minimal importance difference (MID) via the anchor-based approach	+/–	Change scores for improved, stable and deteriorated patients in the expected direction, but some misclassification and small numbers in improved/deteriorated categories. MID for MyPOS total score, improvement: 2.5 MID for MyPOS total score, deterioration: 4.5 Non-significant AUC for Healthcare support
C2) Determining the MID via the distribution-based approach	+	Larger MIDs for total MyPOS score (8.4) and subscale scores (0.8 to 6.2).
Objective d) Acceptability		
D1) Exploring the acceptability of the MyPOS.	+/–	46% MyPOS feasible tool for monitoring 23.9% concerns regarding acceptability, due to duplicate measurement (patients in clinical trials) or symptom monitoring through clinical team.

However, the redundant items that were detected by response-residual analysis represent possible targets for revision. These redundancies mainly concern items in the emotional response and the healthcare support subscales. Some, like the high correlation between the item "depression" and "feeling at peace" are known in the literature and, in fact, both items have been evaluated for their ability to diagnose depression in palliative patients (826). For some of these redundant items, there are clinical arguments to keep them as separate items, such as the items nausea, vomiting, and depression and feeling at peace. The latter, in particular, taps into a different aspect of spiritual well-being that is otherwise not represented by other items in the MyPOS. However, items about family, usual activities and the items in the healthcare support subscale could be possible targets for reduction.

Items in the Healthcare Support subscale caused the most concern from a psychometric perspective. Despite the considerable floor effect seen in those items in the initial validation of the MyPOS, it was opted to keep them in the questionnaire on clinical grounds (384). However, in this second validation of the MyPOS, the healthcare support subscale as a whole showed psychometric shortcomings both in traditional and Rasch analyses (see Table 10). These items were among the misfitting items, showing redundancy and low reliability coefficients, possibly a result of the small number of items in this subscale. Satisfaction can be defined as the extent to which an individual's expectation regarding the quality of healthcare and the quality of information provision are met (827). This definition is not substantially different to the one for QOL that Calman (296) provided, defining QOL as the gap between an individual's experiences and expectations. In general, patient's satisfaction is related to the extent to which general and condition-specific needs are met. The evaluation of satisfaction with care can be argued to be important and clinical relevant because of the consequences of dissatisfaction. Satisfied patients

have been reported to show better compliance with treatment (828), to take a more active role in their treatment (829) and to not change healthcare providers as much (830).

Patient satisfaction has traditionally been assigned a centrality in patient outcomes (831). Donabedian (1966), in his definition of outcomes to judge the quality of healthcare (448), sees patient satisfaction as an outcome of equal importance to HRQOL. However, there is also the opposite view that HRQOL is distinct from satisfaction. Patient satisfaction is regarded an experience measure since it is not only influenced by preceding healthcare but much more affected by personality, socioeconomic background and immutable characteristics of the individual (832). It is thus not considered to be an outcome measure. However, depending on the definition of QOL that guides the development of a measure, these seemingly more distal aspects can be nonetheless regarded as influencing QOL, as is the case in the model by Wilson & Cleary (330). In this model, characteristics of both the individual and the environment simultaneously influence biological and physiologic variables and, through a causal chain linking these elements to symptom status, functional status, general health perceptions, affect overall quality of life (833). We extended this model in our qualitative work by showing that factors of environment and the individual not only influenced the first point in the causal chain, but also influenced every single component forming HRQOL, therefore acting as a lens (357). A link between satisfaction and HRQOL has also been shown in SCT survivors (833). The authors reported a high and unexpected level of HRQOL in these survivors, despite ongoing physical and psychosocial morbidities, a result that was echoed in both the cross-sectional and longitudinal parts of this research. These patients have also reported higher levels of satisfaction with medical care (834) and it was hypothesised that this high level of satisfaction and the reported high level of QOL can be explained by a common mechanism of these patients being more accepting of residual effects which leads to response shift (299). Thus, from a theoretical perspective, there are arguments both for keeping or removing these items from the MyPOS.

The main problem observed in the items of the Healthcare Support subscale of the MyPOS, their unreliability (835-837) and the high undifferentiated levels of satisfaction, are problems often described since the introduction of patient satisfaction surveys into healthcare (838,839). A meta-analysis in 1990 reported a level of satisfaction as high as 80% (840). This led to a general critique of satisfaction surveys regarding their lack of theoretical underpinning and the poor methodology behind their measurement (838,841). Interestingly, several qualitative studies have shed light on the finding of high satisfaction, providing explanations beyond those of an acquiescence response bias in respondents (842). Expressions of satisfaction can also indicate negative experiences and perceptions (556,843), as for some participants, being satisfied with healthcare meant health care being seen as ‘adequate or average’ and not meaning that certain aspects could not be improved (556). In contrast, being very satisfied with a service meant that the

service was outstanding and better than average (556). This suggests a continuum from satisfied to very satisfied, a fact that is not captured at all in the response levels on the MyPOS. The Rasch analysis in our validation work also suggested such an extension of the upper level of the scale because of a non-matching level of satisfaction in participants and the level of discrimination in measurement that the scale allows for each satisfaction item. Of course, the second explanation of those participants in the study representing a biased sample towards those that are satisfied could also be a possible reason for the floor effect observed in this validation. Williams et al. (1998) (843) explained high levels of satisfaction with a perception of culpability. Ferrell (1992) (834) reported feelings of indebtedness to their clinical teams in SCT survivors, leading to more apparently satisfied patients taking part in this research.

Overall, there are arguments both for removing and keeping this subscale. As shown above, these arguments centre around clinical reasons, arguing that dissatisfaction with quality of care is important information (311) and that population-based or routine usage of questionnaires might attenuate the acquiescence response bias inherent in research using convenience samples. On the other hand, these items have repeatedly shown poor psychometric properties and do not satisfy the agreed standards for quality of outcome measures (640). For example, items tapping the domain of treatment satisfaction or relationship with the physician were removed from the initial versions of both the FACT questionnaire, leading to its four-domain core version, the FACT-G (844), and the EORTC QLQ-MY20, previously containing four satisfaction items (310). Since its extension in the number of items, the MyPOS is a comparably long instrument, although it is still a shorter measure than the EORTC QLQ-MY20 (which is combined with the core module, the C-30 (310)) and only a few items longer than the MDASI-MM (690) (see Table 9). Nonetheless, shortening the MyPOS would aid its clinical utility. Regarding the removal of the healthcare support subscale, the loss of information could possibly be compensated by keeping items on information provision and having enough information about the future (items 28 and 33), depression and anxiety (items 14 and 16). Appropriate information provision has been linked to satisfaction and a higher sense of control and coping and overall better HRQOL (845). Dissatisfaction, contrarily, is associated with higher levels of anxiety and depression (846,847). The relationship between anxiety/depression can be bidirectional, with inadequate information provision either making cancer patients more anxious or depressed or depression and anxiety in cancer patients hindering active information seeking or perception of such information (848-850). Dissatisfaction with information provision might be caused by misunderstandings regarding information needs on the side of the haematologist or time constraints leading to unanswered questions (851,852). All of these aspects could possibly be indicated by low levels of satisfaction with information in the MyPOS.

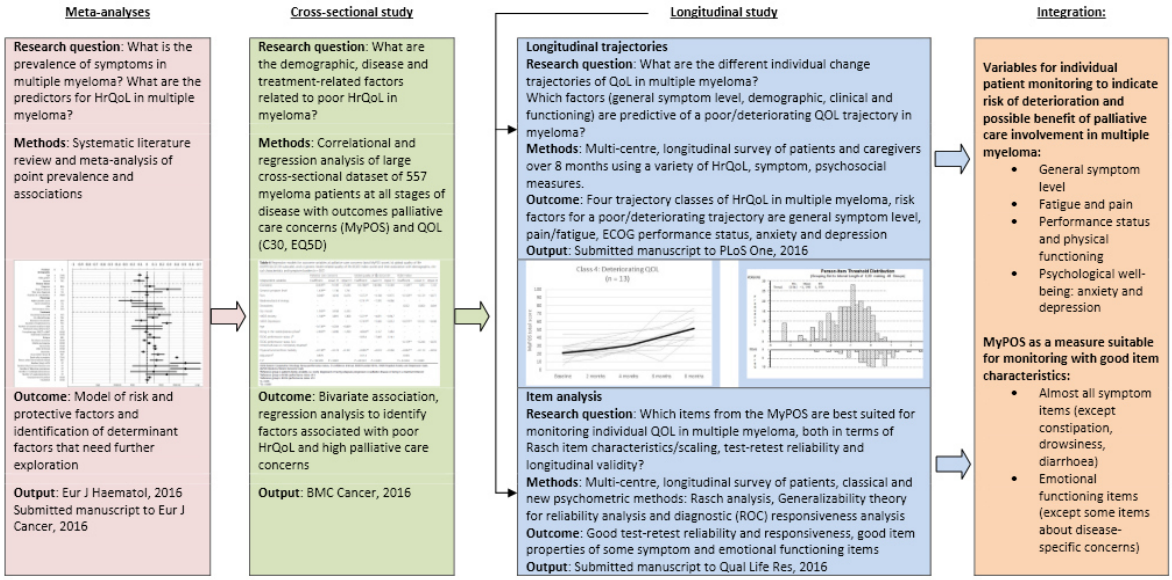
As a last point in the discussion of the MyPOS, a comparison to another generic palliative care measure, the EORTC QLQ-C15-PAL, is warranted because of the similarities between the measures (853). Both the MyPOS and the QLQ-C15-PAL have been developed from already existing scales, with similar aims (to provide short measures for the more seriously ill population) and both using new psychometric methods to do so (395,853-855). However, shortening the QLQ-C30 to its variant for palliative care has resulted in obliterating the social function, cognitive function, role function and financial difficulties scales plus the diarrhoea item (853). These are all aspects shown to be of particular importance in our qualitative work and the cognitive interviews (357,384). Also, the MyPOS aims towards measuring HRQOL in the whole spectrum of myeloma patients ranging from newly diagnosed to patients with advanced and refractory disease. The focus of the QLQ-C15-PAL lies on application in the palliative care setting. However, its advantages include a higher infrastructure around the EORTC measures, involving extensive validation data (858-861), availability of data for norm comparison (711-715), translation and cultural adaptation work (854,862), provision of MIDs and interpretation of cores (368,382,383,863-865), and the recent development of guidelines for the clinical use of their instruments (401). When considering the applicability of a measure, these aspects aiding its use in routine clinical practice need to be taken into account. However, the MyPOS offers items that are applicable in the spectrum of myeloma disease and can be used for longitudinal monitoring, as shown in this psychometric analysis (the validity of the minimal important difference that was derived in this study has been presented in chapter 7 and will be further discussed in section 8.3.3.) The Rasch analysis allowed the identification of items most suitable for such a purpose. Together with the results from the regression analyses, a model of monitoring in multiple myeloma involving PRO parameters can be built.

8.1.4 Integration: Symptom burden, longitudinal changes of QOL and self-monitoring of quality of life in multiple myeloma

Figure 12 presents an overview of the PhD project and shows how the different sub-studies interlink and integrate to help understand who within the multiple myeloma population is experiencing poor quality of life and how these individuals can be identified using individual patient-monitoring and assessment. Describing and understanding the trajectories of health-related quality of life and symptoms in multiple myeloma was accompanied by building a model of predictors in several stages. First, systematic literature reviews served to identify potential explanatory variables and their respective strength of association with the outcome HRQOL were analysed in a meta-analysis. The secondary analysis of a large cross-sectional dataset served to build the first regression models and identifying those variables that explain enough variance in the final model to warrant inclusion. This model was subsequently validated, albeit with the

different outcome variable of membership in the class of poor/deteriorating QOL trajectory and thus combining information from the course of QOL in myeloma with information on risk factors for deterioration. This was complemented by identifying items from a psychometric point of view that are best suited for use in longitudinal monitoring. This analysis tried to answer the same question, but used a measurement quality approach to help identify targets for monitoring in myeloma.

Figure 12: Overview of the PhD research study and integration of findings from different sub-studies



When looking at the combined results of the meta-analysis, the cross-sectional study and the measurement and predictive models from the longitudinal study, it is apparent that those variables that emerged as targets for monitoring in multiple myeloma are very similar to the ones proposed as influencing QOL most strongly in Osborne and co-authors' model of quality of life (357). Their theoretical model sought to represent relationships between clinical, functioning, psychological and health service variables and used Wilson and Cleary's theory of QOL (330) to posit causal relationships between the different domains. The model was derived from patient interviews and focus groups. It is argued that the influence of biological and clinical factors on QOL is less strong than from aspects more proximal to QOL. Even symptoms are seen to not directly influence the outcome, but via a mediated pathway of affecting aspects of functioning (330). This signifies that changes in emotional status, functioning and sometimes symptoms can lead to direct changes in QOL, whereas biological status and treatment factors do not exhibit this direct influence. This relationship was certainly found in this PhD study, both in the cross-sectional data and the longitudinal analysis. It was demonstrated that accumulated symptom burden, mental health and performance status variables indicate who experienced a deterioration or poor QOL trajectory. The psychometric analysis also identified emotional functioning and

coping items as good items for monitoring, thus pointing towards the role of illness adaptation on outcomes. This is contrary to other models (358) that postulate a preponderance of disease- and treatment-related variables on quality of life in myeloma. This study, however, has shown that monitoring should involve patient-reported outcomes since these are more sensitive to capturing deterioration in patient's HRQOL than are biological factors.

The model of predictors and monitoring variables has several further applications. Previous research has highlighted the need for guidelines for HRQOL measurement in MM (359). This model could inform the development of such guidelines for screening and monitoring. It could also be used to identify targets for early intervention, particularly the early integration of palliative care into myeloma care. These aspects are discussed in the sections 8.4 and 8.5, after highlighting methodological limitations and contributions of this work.

8.2 Strengths and limitations of the study

8.2.1 Strengths and limitations relating to the secondary analysis

Secondary analysis of quantitative datasets is a well-established methodology, yielding many benefits but also having implications for the type of analyses possible. My analysis was limited by the measures used to collect the data and the limited demographic and clinical data, particularly on biomedical variables such as haemoglobin, albumin, CRP and beta2-microglobulin. However, the dataset for combination with baseline data from the longitudinal survey that was used for the cross-sectional analysis originated from the initial validation study of the MyPOS (384), and extensive biomedical variables were not important to collect for that purpose. These characteristics, as well as variables acting as mediating factors, as shown in the model of QOL in multiple myeloma (see section 2.2.1), would have enabled me to explore the data with more sophistication, taking more explanatory and confounding factors into account. This might be one of the reasons that the regression analysis on the cross-sectional dataset only yielded an adjusted R^2 of 51.4% for the dependent variables global QOL (EORTC QLQ-C30). Adding these aspects would have allowed an analysis of how psycho-spiritual factors and coping mediated the impact of biological factors and symptoms on QOL, thus validating the model empirically.

The secondary analysis used to build the initial model of predictors was cross-sectional in nature. This might explain the differences seen between the two regression analyses in the size and importance of explanatory variables and their regression coefficients. However, combining the two datasets for building an initial model of independent predictors yielded a much higher sample size, thereby circumventing problems regarding power of analysis. Secondary analysis of datasets always needs to bridge the gap between being confined regarding variables included in the

dataset, since the data was collected for a different purpose, and – under economic and resource perspectives - lifting the full potential of a dataset (551,561).

A major drawback of the statistical analysis of independently associated factors, both in the secondary analysis dataset and the longitudinal model, was the multicollinearity of the factors. Multicollinearity describes the fact that two or more independent variables are highly correlated (which can be the case with PROs), thus leading to incorrect model selection and making it difficult to disentangle the influence of a single variable (866,867). Further testing the stability of the final multivariable model is highly recommended, but this was beyond the scope of this thesis. An approach of controlling multi-collinearity statistically has been followed by one study within cancer QOL research (16,868). A bootstrap model accounting for multicollinearity among several PRO predictor variables was subsequently successfully validated in several studies with solid cancer patients.

8.2.2 Strengths and limitations relating to the longitudinal study of changes of QOL

Piloting was done on a small number of patients that were not purposefully sampled. The sample size was below the recommended target of 10 patients (869). This might have biased views towards higher acceptability of methods used for monitoring than normally present in the myeloma population. Some of the issues that were raised in the pilot interviews questioned the content validity of the MyPOS and scaling issue. So, while most of the relevant quality of life issues were included in this measure, some symptoms were reported as missing. Participants also commented on the scaling of the MyPOS symptom items and pointed towards some redundancy between the MyPOS, the EORTC QLQ-MY20 and the Hospital Anxiety and Depression Scale. However, since these measures were included based on hypotheses regarding the mediating nature of anxiety and depression and with the aim to cover potential aspects and influencing factors on HRQOL in the broadest possible way, the suite of measures was not further reduced for the longitudinal study.

Participants in the small pilot study also pointed towards problems with recall and time frames in the included measures, acknowledging the fluctuation in symptoms and problems depending on chemotherapy and maintenance treatment cycles. The time frame was not altered in keeping with the time frames used in the initial validation of the MyPOS. Validation of this aspect was not within the merit of this study, but it is certainly an area that needs to be explored. Guidance on this issue of time frames and recall periods is rare (583,870-872). Ideally, piloting should involve a sufficient number of patients and caregivers. Caregivers were not included in the pilot study. The longitudinal study was designed such to include information on caregiver burden and the

caregiver's perception of the patient's health status only every four months. This time interval between measurement points was chosen to minimise burden. However, I did not know whether it was adequate for capturing changes in the patient's and caregiver's condition. A pilot study can test whether the planned data collection strategies will work and whether methods of recruitment result in acceptable consent rates as well as determining the acceptability and selection of the most appropriate measures (819,869). This pilot work did not fulfil all of these objectives, mainly due to time constraints. More extensive piloting could have helped design the accompanying caregiver survey in a different way, so that data collection on those participants ceasing to send questionnaires would have been possible.

For the longitudinal survey, inclusion criteria were very broad, thus resulting in a potentially wider and more representative sample of patients to be included, but also biasing the sample towards those patients not suffering from neutropenia. The sample was also biased towards the more stable phases of multiple myeloma since we mainly recruited patients from outpatient clinics. Hospices and other inpatient palliative care facilities were not included in the sampling frame. An alternative would have been to stratify the sample and require a number of patients in each disease severity/phase stratum. This would have resulted in a more balanced sample and allowed the study of mortality. The second possibility would have been to stratify by performance status. However, this would have necessitated including some measure of activities of daily living, such as the Barthel Index (873). In the end it was decided to not include stratification criteria for eligibility to arrive at as natural a sample as possible.

A further limitation in this study is the lack of information on the characteristics of non-participants, patients who were invited to take part in the study but refused. In addition, the denominator population is not known. Describing the study population and the denominator population are essential elements in the study design to judge the representativeness (external validity) and the amount of selection bias likely to have occurred (874,875). Selection bias first occurs when those that take part in a study show different characteristics than those that refused, as likely happened in this longitudinal study which oversampled patients in the stable phases of disease at the end of treatment or post stem cell transplantation. A qualitative study suggested that the feature of a sample biased towards stable phases might be a result of cancer patient's willingness to take part in longitudinal research which is highest after initial diagnosis and treatment when patients are emotionally coping and are not experiencing significant physical side effects of the treatment (586). A second selection bias is introduced through gatekeeping of clinical staff members that performed the screening in the participating centres (876-878). We provided extensive training and standard operating procedures before the start of the study to all study site personnel and in particular to those research nurses identifying and approaching patients for inclusion in the study. However, gatekeeping is still likely to have occurred as evidenced by

the sample biased towards patients not overly distressed by symptoms and psychological problems. Another bias is apparent in the slightly lower mean age that was observed in this study. The mean age of participants was 68.5 years, whereas the mean age of diagnosis is 73 for the UK (55). This lack of older patients has been described as a problem in clinical trials of haematological disease patients (145) and other conditions (147,148). However, the mean age in this study is higher than the mean age reported in clinical trials of myeloma. Overall, selection bias has occurred, but the comparably older sample included in this longitudinal research and the high proportion of comorbid disease in our sample supports the population perspective (145,230).

Ideally, results should be set in relation to the total population served in the recruitment sites. There are two ways to overcome the problem of not having information on the denominator population. We could have asked the research staff at each site to record details of all patients potentially eligible. Since this is a time-consuming process, alternatively we could have collected minimal demographic patient data from those patients that refused to participate. However, the ethics committee did not allow such data collection from non-participants. Another way to reduce and understand the problem of selection bias is to obtain information on the characteristics of the denominator population by performing an audit of all recruiting sites. This approach was hindered by the fact that in some hospitals demographic and clinical information from the patient records was not available in electronic format. For this study, to indirectly judge the amount of selection bias, we compared the demographic and clinical information to other population studies in the literature (90,381,593).

Recruitment into this study, contrary to anticipation and experiences in the field of palliative care, was surprisingly fast and satisfactory. This was possible by using the support of research nurses and research personnel at each site through the infrastructure provided by the National Institute of Health Research who has created National Cancer Research Networks to aid clinical research within the NHS (488). Although setting up the longitudinal survey as a portfolio study resulted in a large sample to be recruited, the bias in participating centres towards tertiary care shows that the population from which the sample was drawn does not represent the population of all multiple myeloma patients in the UK. Particularly community hospitals and hospices are underrepresented. Although the multi-site recruitment helped accrue a large sample of patients that partly counteracted the influence of attrition on the findings, there are concerns about differences in care delivery at the participating sites. While analysing the treatment information, for instance, it became apparent that choice of second- and third-line treatments was centre-dependent and largely driven by participation of these centres in clinical trials. This variation between centres was also observed regarding supportive therapies that patients received, ultimately introducing a bias and influencing outcomes between sites (517).

Caution is required when interpreting the estimates from the regression analysis, owing to the risk of a biased sample. Although care was taken to consecutively recruit patients in the services, in practice those physically better or easier to approach may have been oversampled. There is also some survivorship bias (719) with those patients that have a higher number of QOL-related problems being more likely to drop out of the study. Attrition from the study was moderate with a final 52.5% of those initially recruited returning the last set of questionnaires eight months after beginning the study. This attrition rate is below the one observed in many longitudinal studies in palliative care patients (574,878,879) and also comparable to attrition observed in the most recent clinical trials in multiple myeloma (365,374). Delforge et al. (2012) (365) and Dimopoulos et al. (2014) (374) reported a slightly higher retention rate of 62%, respectively, but their follow-up was determined by the duration of cycles of chemotherapy treatment that was trialed in these studies. Tang & McCorkle (2002) (583) reviewed published QOL studies and noted attrition rates ranging from 27 to 91.4% with an average of 53.6% drop-outs within an average duration of a study of 45.7 days. This rate is comparable to the attrition rate that was observed in our study over a period of 240 days. Attrition due to death was not observed as often as anticipated when planning the study. The main reasons for attrition were questionnaire fatigue and deterioration of the patient, either due to multiple myeloma or due to other comorbid conditions. For a substantial number of withdrawn participants, information on the reasons for withdrawal was not available, despite telephone follow-up. Thus, the small numbers in the trajectory class of poor and deteriorating QOL patients can be attributed to losing patients with worsening HRQOL to follow-up and estimates of change as well as regression coefficients are less stable due to the small sample size in this group (323).

To counteract attrition, I used a number of strategies recommended to promote retention of participants in the study (877). Mechanisms such as personalisation of letters and study communication, thoughtful messaging to make research more relevant, telephone calls and telephone reminders when sending out questionnaires and when questionnaires were not returned, re-sending questionnaires when participants failed to return them and use of incentives with each questionnaire were built into the study to maximise response rates. The method of data collection influences the type of sample that can feasibly be recruited and the characteristics of recruited participants. Postal questionnaires were chosen for reasons of resources, practicability and to obtain data from a multi-site, national sample. The alternative use of face-to-face interviews or interviews over the telephone would have ensured a more personal relationship between participants and researcher, would have resulted in more timely completion of questionnaires and higher completeness of data and might have made it easier to recruit and retain participants for whom English is not the primary language (878,880). Nevertheless, these methods are no guarantee for higher response and retention rates and increase resources and cost considerably for

a longitudinal study of over 200 participants (530,881). Also, although they have proven to be successful in some palliative care studies, they are no recipe for avoiding attrition (878). Views of patients regarding the time point of being approached, the mode of data collection and method of follow-up are mixed, and there are no consistent preferences that ensure good participation. For example, Shipman and co-authors (2008) (585) concluded that face-to-face interviews are preferred over postal data collection, whereas Sherman et al. (2005) (878) and Riopelle et al. (2011) (880) concluded the feasibility of telephone follow-up. Postal surveys have been successfully applied in longitudinal studies within palliative care (587,882,883) and, lately, in registry-based longitudinal monitoring of cancer patients (381,586). In this study, the mode of data collection did not result in an overly large attrition rate and can therefore be recommended for future studies.

Another aspect that reduced the validity of the findings and their generalisability was the issue of missing data (583). Missing data reduces the number of patients available for analysis and particularly challenge the multivariate analysis of the data, as many of these techniques assume complete data and univariate and multivariate normality (884,885). Missing data can occur at the institutional level, at the individual patient level and at the individual questionnaire level (886). The first two parts have been discussed above, handling of missing data from missing forms and missing items will be discussed next. In general, in longitudinal studies and particularly in those in palliative care research, it is impossible to avoid missing data (887). Moinpour (1997) observed that this most compelling setting for QOL research guarantees missing data (888). Hence, the Morecare statement (542) recommended to assume high rates of attrition and missingness in any palliative care data set and to classify reasons for attrition accordingly (ADD – due to death, ADI- due to illness, AaR – at random). The present study was characterised mainly by the types ADI and AaR. This means that a proportion of missing data at follow-up was most likely missing not at random (MNAR) (320), as missing values depended on current or future values. The missing data in this study thus represents non-ignorable missing data.

Strategies to reduce missing data were largely successful and overall level of missing data was low. Missing data was of the non-response type (889,890), i.e. singe items missing. Following recommendation from Hopwood et al. (1994) (891), we tabulated the amount of missing data for each MyPOS item at each time point to graphically portray the size of the problem. Further, we used several imputation methods for missing data in a sensitivity analysis which entailed simple imputation methods (last observation carried forward and median/mean imputation) and multiple imputation. Simple imputation methods have been criticised in the literature for yielding unreliable results. It has been argued that imputation yields a decrease in variability of that particular variable (892). Instead, multiple imputation and Markov Chain models are recommended (610,888,893-898). With the multiple imputation method, varied values are

calculated for a missing value with the sets of imputations repeatedly drawn under one model for missingness and resulting in a combined summary statistic (892). However, even those methods have been criticised for producing invalid results in the presence of missing data not at random (MNAR). The sensitivity analysis yielded similar results with different imputation techniques and the complete case analysis. Three studies of HRQOL in palliative care affirm this finding. In the studies by Ahlner-Elmquvist et al. (2009) (899), Petersen et al. (2009) (900) and Riopelle et al. (2011) (880), non-response did not lead to the underestimation of symptomatology or overestimation of QOL/well-being and different imputation techniques did not result in substantial changes to the results of these studies. Nevertheless, problems with validity and non-ignorable missing data can affect particularly those parts of the sample with more advanced disease. Mor (1986) (901) reported that non-responders in a study of pain and mood states were consistently sicker and more likely to suffer from severe symptoms. Likewise, Hopwood et al. (1994) (899,891) showed that for lung cancer patients, clinician's assessment of functional status was a predictor for dropout, with only 31% of those with poor functional status finishing the study. Twisk (2002) (892) has demonstrated that in a longitudinal situation, using more refined multiple imputation methods did not result in different point estimates than the single imputation methods. Rather, the author recommends using generalised linear models for accounting for missing data in the analysis or alternative approaches for non-linear data (GEE, generalised estimating equation models) that should be tried in a further analysis of the dataset.

Another area of concern is the timing of data collection in this study. Data collection took place bi-monthly to capture changes, but balancing frequent assessments with participant burden was also important to keep participants in the study. Monthly intervals, although in many respect preferable for assessment of more short-term changes associated with treatment side effects and fluctuant symptoms, would have probably obtained smaller changes and data on adaptation processes in patients. In addition, the follow-up period of eight months was not long enough to study long-term adverse effects or long-term changes in patients' coping mechanisms. The follow-up period was much shorter than in some prospective observational research in SCT samples (31,34,35,378,734,902) that followed participants one year to three years. However, since more measurement time points were captured within the eight months, this study provides more information on changes in QOL than other observational research in myeloma (381).

Longitudinal research needs to have three elements to be successful: a theoretical model of change, together with a temporal design and a statistical model that represents or operationalises the theoretical model of change (590). Ideally, the model of change includes a comprehensive statement about the nature of the change phenomenon and the shape of change (linear, quadratic, other forms), as well as the periodicity and/or cyclical nature. The temporal design (timing, frequency, spacing of observations) is one of the components of a longitudinal design that can

have the largest impact on the results (591). While this importance of timing assessments has been stated repeatedly in the literature, its empirical study has not received much attention. Only two studies could be found focusing on the issue of timing QOL assessment (903,904). Due to lack of data on QOL and symptom trajectories in multiple myeloma, the definitions of a model of change in advance was not possible. The lack of certain QOL problems might be due not only to the oversampling of stable patients but also to the mismatch between timing of assessment and recall period of questions with the cyclical nature of patients' treatment-related side effects. The choice of measurement interval can be a determinant for whether an effect is large enough to be detected (591).

Some authors have defined theoretical models that differentiate cancer-related symptoms, acute side effects, chronic side effects and symptoms not related to cancer in their periodicity (871). These models state that the typical side effects in chemotherapy are cyclical in nature, but depending on the treatment, a continuous low level of acute side effects during the treatment cycle is also possible. Added to this are chronic side effects, side effects with a constant or slowly progressing severity, like peripheral neuropathy in multiple myeloma. The model could explain some of the low prevalence rates seen in the data of this study or could explain the lack of problems, i.e. change in mastery of illness, since these aspects of HRQOL might be more trait-like and prone to more stability, necessitating longer assessment periods (833). Klee (2000) (871), together with other authors (870,872,905), postulates different time frames to capture these cyclical symptoms and side effects. In this study, longer assessment periods would have been possible during the stable phases, switching to shorter intervals to obtain information on change in patients with advanced disease or approaching death. Alternative ways of capturing data could have helped with this issue. Online or electronic versions of questionnaires have shown to benefit compliance and recall, also allowing more dynamic assessment of PROs (636,906-910). Online platforms have been successfully used to measure chemotherapy-related side effects (911-914). Electronic data collection was suggested by some participants in the qualitative part of the longitudinal survey. However, using this more dynamic approach to the study of change was not possible in this study, mostly due to logistics. Also, participants in the pilot study argued against changing time frames, preferring fixed intervals so that they could anticipate the next questionnaire and arguing that changes occurred across longer periods, saying that monthly data collection would place too great a burden on respondents and not allowing them to experience a sense of normalcy in between. In this study, I tried to ensure a sufficient number of assessment, but the bi-monthly data collection means that sensitivity to change was partly lost. Also, recall bias might have occurred since any response process relying on cognitive processing and retrospective estimates is less reliable (915).

Similar to the cross-sectional secondary analysis, some explanatory variables are missing from the regression model in the longitudinal study. Next to biological factors, more information on treatment variables would have helped to determine if QOL changes noted were secondary to these treatments. The lack of physiological measures as independent variables is a drawback and makes it difficult to compare this research to other studies in multiple myeloma. However, as already mentioned in section 8.2.1, this data was not available in a reliable and valid format in all participating sites. For example, it was not possible to obtain ISS staging for all patients in the study, due to lack of data on beta2-microglobulin and albumin. Treatment data would have helped to understand the pattern of acute and chronic side effects of treatment, but there was not enough homogeneity in the treatment population to do this. The inclusion of functional assessments in the repeated data collection would have helped to understand changes in HRQOL. The assessment of the ECOG performance status has been included only at baseline and not in follow-up. Assessments over the phone during reminder phone calls could have been used to obtain such data. Alternatively, indices of activities of daily living or the Karnofsky performance status could have been included in the informal caregivers' assessment which would have provided this information for at least part of the sample.

The analysis of trajectories, despite using a novel technique for explaining the heterogeneity that mean trajectory analysis cannot represent, can be critiqued for not modelling change in predictors. Independent variables in the regression analysis did not represent this temporal perspective as variables were taken at baseline but time-varying variables were not included. Furthermore, since prospective QOL information was used mainly for classification of participants into classes of QOL changes, rather than including QOL as a time-varying dependent variables as is possible in general linear models, the analysis did not model predictors of change in QOL.

Part of the wider project was the inclusion of caregivers to collect longitudinal data on change of their quality of life, their views on the quality of life and situation of their partner or parent (by collecting the proxy version of the POS), and caregiver burden. This data was meant to serve as a proxy for deteriorating patients, to allow data collection for those that became too sick or burdened to take part. However, caregivers often stopped returning questionnaires when patients withdrew from the study. Therefore it was not possible to use the caregiver data to inform imputation of missing data in this study. The analysis of the caregiver data is beyond the scope of this thesis but will be analysed and integrated with the results from the longitudinal survey in a future publication.

8.2.3 Strengths and limitations relating to the psychometric assessment of longitudinal validity and reliability

The selection bias already described in the previous section also affected the validation of the MyPOS questionnaire. It is unlikely that participants who find questionnaires difficult and unwelcome have taken part in this study. The acquiescence bias manifested itself in the floor effect that was observed in satisfaction items. The nature of the recruitment process through research nurses working in the recruiting sites and having a long relationship with patients, particularly given the fact that many patients with multiple myeloma can only receive treatment in the UK by participating in clinical trials of new chemotherapeutical agents (i.e. pomalidomide) (82), and potential gatekeeping by healthcare professionals makes it unlikely that dissatisfied patients were included in the survey. The MyPOS is intended as a questionnaire for routine collection of HRQOL in clinical practice. The validity of these questions needs to be studied in a consecutive, routine sample that is free from this bias.

Longitudinal validity and responsiveness assessment either follow an anchor-based or distribution-based approach (916). As anchors, transition ratings, usually regarding the global health or QOL status of the individual, are used. The quality of the anchor, since it is used in a diagnostic approach and a receiver-operating characteristic curve analysis, is determining the quality of the minimal important difference (MID) analysis. As an external criterion it should ideally be free from measurement error (672). However, the amount of misclassification that was seen in Table 5 in chapter 7, ranging from 56.7% in the Symptoms subscale to 94.2% in the Healthcare Support subscale, points towards the global rating of change (GRC) not being free from measurement error. This means that the GRC does not represent a true gold standard and that measurement error is present when classifying patients into groups of importantly improved and importantly deteriorated change (1207). In such situations, it is possible to construct confidence intervals and the area under the curve within ROC analysis using bootstrap (1208,1209) or Bayesian Markov-Chain models (1209). However, these approaches have not been employed within anchor-based responsiveness analysis and are not currently recommended (672,1210).

The anchor that was used in this study only measured change on three levels – improved, stable or deteriorated. In comparison to the global transition ratings used by Osoba (1998) (368,865) with five to seven categories, the anchor in this study most likely lacked sensitivity and discriminatory power. The MID depends on the definition of important change, which in itself is operationalised in the number and labels on the GRC (672). In the Deyo and Centor method (478) that was followed here, the change score on the MyPOS is compared, dividing the population into persons who are minimally importantly changed and those who are not. In studies following this method, different definitions of minimal importance in the anchor have been proposed as either “a little

worse/better" (676,677,1211) to "moderate improvement" (1212) or even "much worse/better" (1213,1214). To date, little research has focused on the amount of "importance" in the change (672,1215). De Vet and other authors (323,687,1216) –rather than considering a slight improvement to be the minimally important change – have proposed to use only "much improved" patients as the anchor for change. The greater the number of levels on the anchor and the smaller the difference between adjacent levels, the smaller the MID will be with the inherent risk of not exceeding the random measurement error (1217). Because of these reasons, the GRC in this study consisted of only three levels – improved, no change or deteriorated. This was thought to help with obtaining clear ratings of change from the individual patient. However, in following a crude approach the analysis forewent capturing the granularity of change and allowing sub-analyses of small changes versus moderate to large changes. Future responsiveness analyses need to explore the optimal number of response levels on the GRC and use cognitive interviewing techniques to understand the standard that is used by patients to make comparisons in their quality of life over time on these anchors.

In general, the transition question did not match the concept of multi-dimensional QOL as measured in the MyPOS. It asked for a global assessment of whether the overall quality of life had changed since the participant first completed the questionnaire. Therefore, the anchor might also be subject to recall bias and response shift (726,917-919) since it asked for a comparison to the baseline assessment instead of the previous assessment. The global rating scale of change asked about change in the same multidimensional construct that the MyPOS is measuring (672). Since its adaptation to the general IPOS format, the MyPOS presents items on disease-related quality of life, but also contains items regarding palliative care concerns. It cannot be determined whether the global rating of change asking about the change in quality of life is interpreted by patients in such a way that change in the same construct that the MyPOS is measuring is assessed. This hampers the analysis of responsiveness since anchor-based approaches using ROC analysis rely on the validitiy and reliability of the anchor chosen. This is a well-described limitation in the literature (672,1218).

The original transition rating designed by Osoba for assessing responsiveness of the EORTC QLQ-C30 (865,869) involved the Subjective Significance Questionnaire. This was developed not as patient self-report, but to be conducted as an interview. This approach, although followed by Kvam et al. (2010a,b, 2011) (368,382,383) when determining the MIDs for the EORTC QLQ-C30 and EQ-5D, would have been too time-consuming and resource-intensive. To aid the analysis of responsiveness different anchors could have been explored. Also, it would have been possible to obtain clinician ratings of change for triangulation with patients' ratings. Suitable alternative anchors include (920): status on a measure of function, physical examination, change in disease severity, response to treatment, and health care utilization. In comparison to the use of a global

rating of change as an anchor, these anchors have the drawback of not representing direct ratings of important change from the patient's perspective. However, the patient's viewpoint is what PROs attempt to express and capture.

It was also not possible to derive an MID for individual symptoms and to test the prognostic significance of cut-off scores for individual symptoms on the MyPOS. To address some of the limitations regarding the anchor-based approach (672), we have followed the approach to test the validity of the anchor by examining correlations between global ratings and baseline and post-baseline QOL as measured on the MyPOS, as recommended by de Vet and co-authors (2011) (478). Spearman's Rho of the GRC with the changes in the total MyPOS and subscale scores ranged from 0.23 (Symptom subscale) to 0.59 (Emotional response subscale) at baseline and from 0.26 (Symptoms and Emotional Response) to 0.41 (Total MyPOS score) at follow-up. These moderate correlation coefficients point towards a statistically significant correlation between the GRC rating and the score changes, which is deemed necessary to accept the validity of the rating score (682,1216,1219). However, some of these correlations between the global rating scale and subscales of the MyPOS also highlight that the phrasing of the GRC might have precluded this scale to validly assess change in aspects such as symptoms and some functioning aspects in patients.

Distribution-based methods for obtaining MIDs were contrasted with the anchor-derived estimates (916). Within the latter approach, distributional characteristics of the sample express the observed change to a standardised metric, for example effect sizes. The disadvantage of distribution-based methods lies in their inability to provide an indication as to the importance of observed changes (916). Following Crosby et al.'s (2003) (672) recommendations, we combined anchor-based and distribution-based approaches and checked how well estimates from both approaches align. The distribution-derived MIDs are well above the anchor-based MIDs, highlighting the likely high misclassification when using the anchor-based MIDs in this sample. Finally, we also related the anchor-based MID to the standard error of measurement (SEM), thus checking that obtained MIDs exceeded the imprecision of the instrument (682). The SEM for the total MyPOS was 6.9, and 3, 5 and 1 for the subscales Symptoms, Emotional Response and Healthcare Support, respectively. The estimated MIDs for the MyPOS do not exceed the SEM for the total score or the subscales. Therefore, MID estimates are likely biased and should be determined with an alternative anchor or GRC scale in the future.

In the Rasch analysis, it would have been beneficial to do more extensive testing of the unidimensionality assumption of each subscale. This was partly checked by re-running the confirmatory factor analysis. These tests should have been supplemented with procedures available within the analysis (i.e. principal component analysis (663,668)). Before proceeding to

more advanced longitudinal applications, revising items with reversed thresholds in category probability curves, revising items showing poor fit and using differential item functioning (DIF) analysis to check item bias would have elucidated areas for further revision of the MyPOS.

Although the use of the Generalizability approach for assessment of test-retest reliability represents a novel approach to the measurement of change in palliative care, interpretation of the reliability indices is difficult. Guidelines for the interpretation of the size of the derived indices, particularly the one for within-person change, are needed. I followed standard guidelines (640,921,922), but experience with these indices is lacking. The framework of Generalizability theory assumes frequent measurement. The approach that was followed in this analysis was originally developed for daily measurement of emotions via diaries. The timing of assessments in this study, every two months, benefitted trait-like change in HRQOL (870). It would be beneficial to test this framework in a situation with more frequent measurements of QOL. For reliability testing, only stable patients were considered that self-identified as stable in the global transition rating. The misclassification that might have occurred in the anchor was already mentioned above.

All analyses of longitudinal validity and reliability were performed on non-imputed, complete case data. For the derivation of the MID and test-retest reliability, two analyses were performed – contrasting time point 5 (the last available time point) with baseline and contrasting time point 2 with baseline. The latter comparison formed the basis for deriving the MIDs following the anchor-based and distribution-based approach and for deriving test-retest and further reliability estimates according to Generalizability theory. This was necessary because of small numbers with complete data in time point 5, pointing towards the attrition of over 40%. It was decided to not impute missing data despite the complete case analysis being biased towards those participants with a higher quality of life and less disease-related deterioration. Despite efforts to ascertain reasons for withdrawing from the study, the mechanism of missing data (see classification and discussion of multiple imputation methods for longitudinal data in section 8.2.2.) was not known for most of withdrawn participants and in the absence of further clinical data, missing data could not be imputed in a valid way. This highlights that longitudinal validation of the MyPOS was only performed on those with better quality of life and not those more severely ill or in a later disease phase.

One of the limitations of the assessment of the acceptability and utility of longitudinal monitoring was the limited data quality. Questions about these aspects were asked in an open-ended nature in the third questionnaire. Participants were provided with open questions regarding the suitability of the MyPOS for longitudinal monitoring, their willingness to self-complete such measures frequently before clinic visits and a question regarding preferences for data presentation. However, these questions were asked in a survey and were not explored in-depth with

participants. Studying these aspects in a routine care environment using qualitative interviews would yield richer data. This is an area for further research.

8.2.4 Ethical issues

Unusually high participation rates in bone marrow transplantation studies, as high as 86-100%, have often been observed (923-925). However, the myeloma population, subjected to frequent treatments with a high impact on QOL, represents a vulnerable population and researchers need to be sensitive in their approach to potential participants who may sacrifice autonomy because of a sense of indebtedness. To minimise coercion, the initial approach was led by research nurses at participating centres who were usually not a member of the participant's primary care team at the hospital.

It is recommended that in longitudinal studies continuing consent is taken from participants (926), seeing informed consent as an on-going process in the potentially distressing situation that answering questions about their well-being or lack thereof constitutes for patients (927). The issue of repeated consent was of lesser concern in this study since participants could choose to not return their questionnaire. However, continuing telephone contacts and reminder calls were of greater concern and I continually checked with participants that they were still willing to continue with the study.

In addition, researcher intervention in the presence of high levels of symptoms or psychological distress was mandated by the distress protocol in this study. The distress protocol was activated twice during the course of the study, once because of suicidal ideation mentioned by one participant and another time when a patient mentioned a serious side effect from the anti-cancer treatment. Both cases were brought to the attention of the clinical staff caring for these patients at the participating sites immediately. However, since data was collected in a postal way on standardised forms with not all participants taking the opportunity to qualify their status by making use of the additional comments field at the end of each questionnaire booklet, some instances of distress could have been missed. All the participants in the study were under regular follow-up in their hospitals.

Overall, completing questionnaires containing personal questions about emotional and sexual well-being repeatedly every two months was not perceived as overly distressing by most participants. However, a few comments in the open-ended questions on the MyPOS and the additional comments section at the end of the questionnaire indicated that for some participants, completing a questionnaire about their well-being served as a reminder of their disease and mortality. However, this situation is not avoidable. The ethics committee reviewing the study did

not voice concerns regarding this aspect. Rather, they advised to increase the sample size to allow for valid estimates to be obtained and not waste resources by conducting a study that is under-powered (see Appendix A, Correspondence with the Research Ethics Committee: approval and amendments).

8.3 Methodological contributions

8.3.1 Recruitment and retention of participants in a longitudinal palliative care study

This thesis has developed longitudinal techniques and developed successful ways of keeping participants engaged with the study. There is still a dearth of longitudinal population-based studies in haematology and in multiple myeloma specifically. Those studies that recruit a population-based sample either utilise cancer registries for identifying potential participants (381) or follow patients undergoing stem cell transplantation (29,34,35,378,496,928,929). Despite the sample in this study being weighted towards stable phases, one quarter to one third of participants experienced advanced disease, relapsed and refractory disease. I managed to keep these participants engaged with the study over the period of eight months, despite the fact that most of these participants were not recruited by myself personally and that postal surveys have a lower participation and retention rate than interview-based studies (880). The need for longitudinal studies has been recognised in palliative care research (930), but studies employing this methodology have traditionally reported problems with recruitment and retention of participants (574,931).

In the methodological literature, recruitment/enrolment and retention as well as minimisation of missing data are often treated as separate entities with different strategies proposed for these phases of research. Strategies identified to overcome difficulties with ascertainment and enrolment comprise using clinical criteria and medical record review instead of physician prognostication, and personalised recruitment letter content from the patient's personal physician with personalised brochure/information leaflet content (932). The UK National Cancer Survivorship Initiative commissioned a study to understand when best to approach cancer patients for inclusion in longitudinal monitoring of PROs (586). In this interview study with patients and clinicians, optimal time points for recruitment were perceived to be after initial treatment had finished, provided that patients were coping emotionally and were not suffering from significant side effects of treatment. A qualitative study to understand participation in a longitudinal postal cohort survey recommended providing clear information about the study and explanations of the likely benefits. The neutrality of the survey and its origination from a reputable source were further determinants of participation (933). Some randomised trials have tested different aspects

of survey design to enhance retention and completeness of data, among them strategies like shortening lengthy questionnaires (934), sending full reminder packs (934), using a different mode of contact for follow-up and reminder phone calls or phone interviews (935). Recent systematic reviews of 481 RCTs evaluating 110 different methods of increasing response rates to any survey found factors such as incentives, personalised letters, pre-questionnaire contact and reputable source (university rather than governmental or commercial organisation) being effective (936,937). General ways of enhancing participation and thus retention in an intervention trial in palliative care employed strategies such as systematic tracking and phone calls, minimising respondent burden and maintaining interviewer-respondent dyads over time (880).

In this study, rather than treating enrolment, retention and minimising missing data as separate entities, the researcher developed an overall strategy to engage participants and keep them engaged with the study. Especially given the fact that recruitment was performed by the research nurses at the different sites, a strategy building rapport and personal relationships was thought to be of primary importance for the success of the study. The fact that many research nurses in the participating sites also worked as clinical nurse specialists meant that they already had a personal relationship with the patients, a fact that has helped recruitment and enrolment. The researcher then called each participant after receiving the first questionnaire, explaining further about the study and getting to know the participant. Every study communication, particularly the letters accompanying questionnaires and reminder packs, was personalised. The researcher kept a log book of phone conversations and significant events about the participant's wellbeing and used this information when contacting participants. Each questionnaire that was sent to participants came with a pen and a little sweet, following advice from Bowling (2000) (580). Rather than giving monetary incentives, the sweet was perceived as a little treat and some participants even took the trouble of calling the researcher to request certain sweets to be sent with the next questionnaire. If questionnaires were returned with incomplete questions, the participant was called and asked about the reasons for the missing item or pages. The questionnaires in the questionnaire pack were preceded by instructions for completion and highlighting the importance of complete data and correctly completed questionnaires. If questionnaires were not returned after a reminder and a full questionnaire pack had been sent, the researcher or one of the research nurses contacted the participant by phone to ask about reasons for withdrawal from the study. Recruiting patient and caregiver dyads certainly helped keeping participants interested in the study. Some informal caregivers commented that they valued being asked their views and that they convinced their partners to continue with the study even if that participant felt inclined to withdraw because of deteriorating disease.

The overall strategy of personal contact and keeping this contact over a period of eight months with each participant has likely helped to maximise and maintain follow-up. Especially the

methods of personalised letters, sending out letters with a hand-written greeting and signature plus a photograph of the study team at King's College London, telephone contact both initially and after completion of questionnaires in case of missing data or potential withdrawal and sending out questionnaires with a pen and a sweet proved particularly successful. Although this approach to longitudinal monitoring is time-consuming and resource-intensive, it does help to overcome the barriers associated with longitudinal research in palliative care and particularly it helps remedy the low retention rate and high level of missing data reported in palliative care research (574,931) and observational haematological research (95,381). These techniques should be considered in future studies. Recommendations for handling missing data usually focus on statistical imputation methods, but rarely name strategies to minimise them at the level of data collection (938). Strategies to overcome missing data recommended by researchers entail using interviewer-based questionnaires as mode of administration (880). In this study, rather than using phone interviews, we used postal surveys but with a telephone follow-up call if questionnaires were returned incomplete. This is a practical strategy seldom used in research which could be explored further.

8.3.2 Latent growth mixture models for modelling heterogeneity in palliative care

This study made a methodological contribution to palliative care research by being the first within the context of longitudinal studies in advanced cancer to employ latent growth mixture modelling and latent class analysis to QOL data. Advanced illness is a continuing and chronic experience with the impact of various clinical, disease- and treatment-related factors developing over time. The ability to model change and explore trajectories of QOL using advanced statistical techniques depends on large enough datasets. Therefore, the methods developed to maximise recruitment and retention in this study directly helped to bring a higher sophistication to the longitudinal analysis than normally possible in palliative care research. Longitudinal studies in advanced disease are usually limited by small numbers and a high volume of missing data (931), however, more descriptive and older analytic methods such as repeated measures ANOVA or simply computing rates of change, thereby presupposing only linear trajectories over time, have been shown to be outdated and producing biased and misleading results (939). Small sample sizes have often limited longitudinal analyses to descriptive graphing of results only (155,587). While exploratory and confirmatory graphical analysis is certainly valuable in its own right and recommended as a first step to longitudinal analysis for screening raw data and understanding possible inter-relationships in the data (940,941), failure to use analytical techniques can result in non-detection of important covariates and confounding factors. Other outdated methods that have been used in recent longitudinal palliative care studies are: change scores (as a single number per subject indexing change instead of treating change as a continuous variable) (574), repeated measures

analysis of variance and analysis of covariance (942). In the former approach, the problem of analysing longitudinal data is essentially bypassed by summarising change for each subject with a single numeric value that is then used in further regression analyses. A major drawback of this method is that coefficients are assumed to have equal reliability, even in the situation of incomplete data (386). Similarly, repeated measures AN(C)OVA requires evenly spaced repeated observations and complete data across subjects and time points, an assumption that rarely holds in palliative care research (542). Also, within-subject data over time results in auto-correlation of observations which also violates the assumption of non-correlated error in ANOVA (386,943).

Given these drawbacks, newer, advanced techniques of longitudinal analysis are recommended, of which the two most common approaches are random-coefficient models (944) and generalised estimation equation models (GEE) (945). Random-coefficient models, also named mixed-effect models, estimate a straight regression line (if linearity is assumed, otherwise other rates of change can also be modelled, i.e. quadratic or cubic change) for each subject in the sample. Covariates are then added to the model, of which there are two types: subject-level fixed (constant) covariates (e.g. demographic or clinical variables, coping styles) and within-subject time-varying random covariates (e.g. time-varying biochemical variables, symptoms) (594,946). Added to this can be interaction terms between the covariates. However, these models work by essentially estimating an average rate of change for the whole group (i.e. a mean trajectory of change). Advantages of this method are its flexibility in terms of handling imbalanced data (with different time points per subjects and variation in the timing/spacing of observations) and missing data. This is achieved by usually employing maximum likelihood estimators which correct for certain types of missing data (missing completely at random and missing at random) (947). Recently, this method of longitudinal analysis has been used to describe trajectories of physical symptoms, coping styles and quality of life and their interrelationships in the last year of life of ovarian cancer patients (948). In this study from the Australian Ovarian Cancer group, a mixed effect model including time to death as fixed effect and coping styles as random effects was fitted to each of the 16 subscales of the FACT. The coping variables higher optimism and lower helplessness emerged as significant predictors for better QOL at the end of life (948).

A different approach to longitudinal analysis was followed by Spichiger et al. (2011) (573) in their prospective study of symptom prevalence and its changes in patients with advanced cancer. They used a model of generalised estimation equations with the number of symptoms as outcome variables, time as main predictor variable and controlling for depression as measured by the HADS-D as a confounding factor. GEE models (600) approach longitudinal analysis using a top-down approach (386), unlike random coefficient models which focus on individual subjects, and then average processes of change. GEE models directly estimate the changes in the dependent variable over time (600). Their advantage over random effects models is the ability to estimate

non-normally distributed dependent variables. Although both methods are powerful methods for longitudinal analysis of change, they assume that subjects are drawn from a single population and that a single trajectory of change can adequately approximate and represent an entire population. It is therefore also assumed that covariates affecting the trajectory of change influence each individual in the sample in the same way. Within the mixed effect framework, methods can be used to separate out between- and within-subject relations, but heterogeneity in trajectories is not modelled (386). However, describing an entire population with known heterogeneity like the type of myeloma disease, stage of disease and treatments received using a single trajectory estimate likely results in an oversimplification of the complex pattern of change among members of different groups in the sample.

In this study, the focus was on understanding the heterogeneity of QOL trajectories and particularly understanding who experienced a poor outcome in terms of poor HRQOL and high symptom burden. The aim was then to identify variables that indicated who was at risk of experiencing low QOL in multiple myeloma. Consequently, instead of following a conventional approach of estimating a single average trajectory, estimation of variance and assuming a uniform influence of covariates on the variance and growth parameters (949), the aim of the study called for modelling heterogeneity in the sample. The goal was to classify individuals into distinct groups based on their individual QOL trajectories over time, thereby identifying groups or classes of individuals with a distinct pattern. Such an analysis produced groups in which individuals within one group were more similar than individuals between groups (949). Latent class growth analysis (LGCA) can be understood as a person-centred approach to longitudinal analysis rather than being variable-centred, in which the goal is to identify significant predictors and describing interrelationships between and among independent and dependent variables. This analysis produces separate trajectory models for each class of subjects, each with its unique covariate influences (608).

Variability in symptom trajectories has traditionally been modelled in child development studies. Latent class growth analysis and growth mixture modelling (GMM) have only been recently introduced into longitudinal descriptive research in cancer and wider healthcare. Kroemeke (2016) (950) studied the association between distinct patterns of depression and coping variables in myocardial infarction over a period of 6 years. She found four latent classes of depressive trajectories. Membership in the chronic depressive trajectory class was associated with negative coping strategies. By testing a model of four trajectories of depressive symptoms over time, chronic high symptoms, rising moderate symptoms, fluctuating symptoms (decreasing – then increasing) and low stable/decreasing trajectories, she was able to explain the inconclusive results seen in research to this date (950). This study showed that classes of trajectories help elucidate inconsistent results that stem from studies using mean symptoms scores for the entire sample,

particularly in a scenario where subgroups exist, each with a different level of symptoms within an overall heterogeneous sample of patients. However, given that it is likely that patients adjust to the disease, its impact on their HRQOL and treatment-related effects over time depending on personal and other characteristics, cognitive appraisal and coping, the presence of one common trajectory of symptoms over time is an unlikely situation. LGCM and GMM analysis allow the description of homogeneous subgroups whose trajectory can be characterised by intercept (low, middle or high level of symptoms), slope (decreasing, increasing, fluctuating or stable trajectory) or both (combination of severity and shape of trajectory). GMM models can serve the function of testing a certain theory of change (590), such as the stress and coping model (343).

Latent mixture growth modelling was also successfully employed in Parkinson's disease (606). The research group had first analysed mean trajectories of generic and disease-specific QOL in this condition, using both the EQ-5D and the Parkinson's Disease Questionnaire for modelling. A multi-level mixed model, a variant of a random coefficients model (597,951), was used to estimate the mean trajectory of change and to explore predictors of change. The authors subsequently wanted to model the considerable heterogeneity in individual trajectories both on the generic and the disease-specific outcome measure. Also, since the assumptions of mechanisms of missingness and equal variances and covariances of the outcome variable over time were violated in their initial analysis, they re-analysed trajectories of QOL. This analysis demonstrates the feature of LGCM of accounting for missing data in the dependent variable through the full-information maximum likelihood method under a missing at random assumption (952). The only study in cancer research using such an approach studied patterns of change in supportive care needs and psychological distress over a period of 8 months post completion of initial treatment in breast cancer patients (953). Four trajectory classes were identified, among them two indicating high or increasing needs and psychological distress. Predictors of coping variables and treatments received helped predict class membership. The study was the first to study trajectories of supportive care needs.

Compared to these examples, this study is the first to employ the technique of LGCM to study HRQOL over time in multiple myeloma and thus among advanced cancer patients. It utilises this new approach to understand the considerable heterogeneity in individual trajectories, to combine person-centred techniques of identifying homogeneous groups of trajectories (601), and also circumvents some of the problems around handling of missing data and non-evenly spaced observations over time that characterise random coefficient and GEE models (954). It allows the study of how predictors differently affect only certain types of trajectories. Other than Klotsche et al. (2011) (606) and Brédart et al. (2014) (953), in this study only predictors for deteriorating and poor QOL were modelled, using logistic regression analysis. Subsequent studies could examine predictors for the remaining two latent classes. This is further discussed in section 8.5.1.

8.3.3 Psychometrics for monitoring quality of life

Similarly to bringing new approaches to the analyse of change in HRQOL over time into palliative care, another methodological contribution concerned two new techniques of psychometric analysis for understanding the longitudinal validity and reliability of the Myeloma Patient Outcome Scale.

The aspects of QOL and palliative care concerns, particularly aspects such as symptoms and psychological distress or coping variables, are dynamic processes with constant change. Monitoring QOL thus has the potential to provide high-resolution information about evolving processes of adaptation and progression of symptom burden. However, frequent measurement as it occurs in the context of individual patient-monitoring can place substantial demands on participants. This burden should be minimised by the use of shorter questionnaires, yet this approach sacrifices reliability through diminishing redundancy with which a domain of interest is measured. This might also restrict the conceptual range of the measure. Since the measurement of change came into the focus of psychometrics (955,956), unreliability of measures has been shown to diminish statistical power that can lead to biased influences (957). This is of concern when measures are used in clinical monitoring, were relatively small variations need to be detected when studying intra-individual change. Through the loss of power this issue also affects clinical trials and detecting between-person differences in outcome measures (649). The usual approach is to use longer measures for the study of change, a strategy that is not favourable in palliative care where shorter measures are preferred due to the sometimes quite considerable level of impairment and fatigue that patients experience (316).

Since this study used the MyPOS over a comparably long period of eight months, this measurement framework provided the opportunity to study the reliability of the measure using Generalizability theory (GT) (659). Generalizability theory is a new extension of classical test theory, using analysis of variance to decompose the variance of a set of scores into multiple effects and their interactions plus an error component (656). Generalizability extends the reliability estimates within classical test theory. Reliable indices of measurement consistency range from 0 to 1. Essentially, reliability estimates such as coefficient alpha (958) or intraclass correlation coefficients (ICCs) gleaned from test-retest reliability analyses try to quantify the amount of random measurement error. The reasoning behind this assumption is that in classical test theory (CTT), a person's true score is always constant. Observed scores vary from one measurement occasion to the next. If there is little variability in observed scores, each observed score is close to the true score that is unknown. Reliability is high if the correlation between observed and true scores is high.

Although coefficient alpha is perhaps the most widely used reliability index, its use has been contested for a long time. Even Cronbach reflected 50 years after its invention that it may be a useful but certainly a limited tool for practice (959). As becomes apparent from the description above, CTT treats all error as random measurement error. Cronbach himself introduced a theory of generalisability in 1972 (659) that makes it possible to assess multiple sources of measurement error in order to pinpoint these sources of error, disentangle them and estimate each one individually (656,659,960). Cranford et al. (2006) (651) used the GT approach to decompose the item variance into the different components item variance, time variance, person variance, and the interaction terms (person by time variance, item by time variance, person by item variance), and error. From these components they estimated four types of reliability. Among them are types of alpha coefficients for a person on a single day and for persons over multiple days, but GT also allows assessing the precision of the measurement of systematic change in a person. The typical palliative care patient experiences constant variation over time. Classical reliability indices cannot take this variation into account. They treat it as error which diminishes the reliability of the measure. The new approach represents a solution for this dilemma and allows the estimation of reliability even in an environment of constant change. Cranford's approach is not the only one available, other authors have used other forms of GT (960) to develop different methods of assessing within-person change (651,660,961-963). However, Cranford's method provides two indices that are of particular importance for assessing a measure's suitability for individual patient-monitoring: the estimate of reliability of measurement on a single day and the estimate of reliability of change. These indices essentially capture how much trust a clinician can place in the interpretation of scores of a patient when s/he sees that person in clinic and whether the measure can capture the change in the patient's condition that is happening over time, thus providing an estimate of sensitivity of the measure. This was therefore used in determining the suitability of the MyPOS for monitoring.

It is also possible to marry GT approaches with item response theory, either by using embedded or sequential designs. In a sequential design GT is first used to identify important sources of variation which are then further understood by diagnosing aberrant persons or items that exhibit floor or ceiling effects (964). In this study, I did not follow such an approach but rather performed a Rasch analysis of the MyPOS subscales, together with using the new psychometric approaches for sensitivity and responsiveness analyses. However, the two methods still interlink in producing a general assessment of the measure's suitability for monitoring QOL in multiple myeloma. As such, in this study I tried to show that psychometrics can help assess the clinical utility, namely the measure's suitability for routine clinical use. Psychometric evaluation to support clinical use is a relatively under-developed conceptual field. Evidence of validity, reliability and responsiveness is requested by both practitioners and the community to form a judgement on the instrument's

appropriateness (965,966). However, the exact psychometric criteria for the application in clinical practice are ill-defined. Recent guidelines (287,640,641) mainly define the psychometric methodology for supporting research applications. Only one conceptual paper could be located that proposed criteria for individual patient-monitoring regarding (i) the interpretability of scores, (ii) assessing the full range of underlying constructs across different age groups, diagnoses, severity and comorbidity, (iii) minimal floor and ceiling effects, (iv) reproducibility and minimal measurement error over time for individual patients, and (v) sensitivity to clinical change (649). The authors also recommended more stringent benchmarks for measurement errors for longitudinal use of measures (649). Moreover, evidence to support the psychometric properties of outcome measures is often gleaned from clinical trials, rather than using observational studies that can provide a better representation of the 'messiness' of clinical data (436). Particular attention is placed on measurement precision and sensitivity to change in this context (649).

Rasch analysis offers one solution to address these shortcomings. In Rasch analysis (662) a measurement model is defined which allows summating scores into an overall score per unidimensional subscale. The Rasch model assumes that the response to an item is only defined by two factors; the person's ability to answer the item and the item difficulty (662,967). The probability of a given response is a logistic function of the relative distance between the item difficulty (item location) and the respondent's location (person ability) on a linear scale (968). In health care, person's ability can be thought of as the person's level of a certain symptom, i.e. pain or anxiety, whereas item difficulty is the level of pain or anxiety severity that is expressed by the item. Transferred to QOL measurement, responses in a QOL tool such as the MyPOS are only determined by the health status or quality of life of the person and the level of QOL or health status impairment represented by the item. A questionnaire that meets this requirement exhibits certain features that overcome some of the problems associated with the CTT approach. First, questionnaires constructed under the Rasch model have interval scaling properties. Rasch analysis provides estimates of measurement sensitivity and scale discrimination and also reflects the fact that precision and scale discrimination are not constant across all levels of a given score distribution. Especially QOL measures with comparably fewer distinct levels on the scale tend to yield skewed distributions and floor and ceiling effects (283). In Rasch analysis, it is possible to understand the reasons for these floor or ceiling effects and thus reasons for the mismatch of the ability level demonstrated by the sample and the difficulty level represented by the QOL scale. This is because Rasch analysis allows disentangling scale statistics from the particular sample from which they were derived (665,969). Thus, obtained statistics in Rasch analysis are sample-independent and indicate which items can be used in which type of sample, i.e. certain items are fitted to persons with a comparably low level of QOL whereas some are appropriate for those experiencing minimal symptom burden or psychological problems. This also improves reliability

of the scale (666) and even allows the direct comparability of scores from different QOL questionnaires through equating different measures with one another (283). A future application of Rasch analysis could involve equating a total score on the MyPOS with a total score on the EORTC QLQ-MY20, for example.

CTT is the paradigm under which the MyPOS was constructed and evaluated. The Rasch analysis of this measure revealed important areas for revision. It helped to understand the considerable floor effect that was seen in the health care satisfaction items, demonstrating that the sample was ill-matched to the level of difficulty of the items. It also showed that some items on the MyPOS were not suitable for individual patient-monitoring. Particularly some items of physical symptoms and the emotional response scale did not exhibit a Guttman pattern (970). Some items also demonstrated item bias by showing differential item functioning (971). DIF shows instances of the scale not working in the same way for all groups being assessed. This means it tests if the items of the scale are invariant across all possible levels of QOL severity and invariant across the clinically relevant groups in which they are used (i.e. groups of different stage of myeloma disease) (972). This type of analysis was used in a way initially proposed by Hobart (2009) (661) to evaluate responsiveness. He also proposed to use DIF analysis to understand test-retest reliability but since I used GT analysis in this study, which provided a more fine-grained approach, Rasch analysis was only used to understand sensitivity to change and responsiveness of the MyPOS. This approach addresses almost all the parameters for the adequate psychometric analysis of individual monitoring as proposed by McHorney & Tarlov (1995) (649).

Cited as a major drawback for the clinical applicability of QOL scales, the interpretation of the significance of differences or changes in the score in a particular QOL domain (687,973) have posed a challenge to developers of health status measurement scales for a long time. Individual patient-monitoring of QOL poses the challenge of focusing on change data at the individual person level, a challenge that cannot be addressed by employing methods of CTT (283,974). The added value of Rasch analysis in this study stems from its ability to disentangle the potentially confounding variables of the performance of the scale with persons' level of QOL, as described above. In addition, Rasch-based estimates provide individualised standard errors, thus providing statistics at the level of the individual patient. In CTT, significant change for any one individual is often treated as a simple function of the magnitude of change in the sample used to derive the minimal important difference (636,672,687,920,974-976). Rather, Rasch analysis shows that the significant change in individuals also depends on their location on the continuum at all measurement time points (661). Often, measurement precision and presence of floor and ceiling effects can make the derivation of the MID impossible. Rasch analysis, not relying on group-level variance of scores or standard error as the denominator, is able to detect differences by using the standard error of scores for individuals (661). It thus provides a framework to understand which

items are suitable for individual patient-monitoring, an objective defined for this study. This approach to constructing or revising scales is relatively new to health services research and the validation of HRQOL questionnaires. Research groups around Jeremy Hobart (661,663,977), Alan Tennant (668) and Richard Siegert (978) have used Rasch methods for scales in palliative care or non-cancer conditions at the end of life (interstitial lung disease, multiple sclerosis (979)). Although the Rasch measurement model addresses many of the shortcomings of a classical test theory approach to responsiveness, the high level of statistical and measurement knowledge it presupposes on part of the reader makes it difficult to translate its benefits to practitioners who are the ultimate addressees when arguing the clinical applicability of a QOL scale in monitoring. However, this thesis shows that it can be used to provide solutions to some of the taxing issues regarding validation of the scales in a field such as palliative care.

8.4 Clinical recommendations: Improving QOL assessment and palliative care involvement in multiple myeloma

8.4.1 The use of MyPOS in research

This thesis set out to study the clinical applicability of a measure of QOL and palliative care-related concerns in multiple myeloma. Specifically in the validation I focused on measurement characteristics showing that the MyPOS is suitable for longitudinal use as it occurs during patient-monitoring or in clinical trials. Only recently has PRO use been advocated in clinical trials by the FDA and the EMEA in their guidance documents (287,637,980). The industry-sponsored PRO use centres around inclusion in phase II and phase III clinical trials (981). However, a review of trials registered on clinicaltrials.gov has shown that only 12-15% of protocols for phase III studies incorporate some form of PRO assessment (982). This incorporation, almost exclusively as secondary endpoints, is largely driven by the potential for securing a labelling claim in the USA or in providing arguments for reimbursement in Europe (981). This perspective disregards the fact that regulators and payers are only two of the stakeholders, with clinicians and patients being the key stakeholders. Moreover, the number of RCTs including PRO as an endpoint is still much lower in haematological trials than in trials of solid cancer patients (24,983). At the point of the review in 2009, only 15 clinical trials that included QOL outcomes in myeloma could be located. These outcomes are often published separately to the main findings (82,365,366,374), which makes linkage of information on progression-free survival and potential QOL benefits or treatment-related toxicities difficult. This practice is in stark contrast to the situation of patients with multiple myeloma who represent a group with incurable disease with an impact on patient's wellbeing over a prolonged period of time. QOL data can be most informative in diseases where treatment-related toxicities are of interest or treatments are expected to be more palliative than

others (888). In myeloma, prolongation of the progression-free interval is often considered as the primary outcome with patient-reported QOL assessments being relegated to second place (24,983). Failure to include PRO assessments in advanced stage, however, can result in misjudgement of the effects of a trial (554). Recognition of this complexity underscores the importance of including information on HRQOL in clinical trials in multiple myeloma and haematology.

The use of the MyPOS as a disease-specific QOL assessment tool particularly targeted at later disease stages is recommended as at least a secondary endpoint in clinical trials. Its potential value lies in capturing additional treatment effects, providing valuable information on the patient experience and adverse effects of treatments. Studies in haematological cancers (22,23) show a linkage of physical functioning/fatigue and survival. HRQOL information thus may provide additional information for predicting prognosis and outcome in clinical trials. Finally, the MyPOS could be used to understand interactions and trade-offs among symptoms (288).

Certain features of the MyPOS support its use in this context. Three free-text questions about main problems/concerns and three free-text fields about additional symptoms could help identify the most concerning symptom or problem in patients, an approach that is put forward as a new way to analyse longitudinal data in palliative care (574). In addition, the free-text format can provide additional information on why certain items are missing. This is particularly valuable in the context of palliative care where one methodological concern centres on the often high amount of missing data (520,542). The MyPOS assembles the most important symptoms, derived from extensive patient interviews (357). In clinical trials, it can provide a brief assessment of the most important tumour-specific symptoms in myeloma, either shifting the focus to symptomatology in trials of anti-myeloma therapy or helping to promote the evaluation of supportive care interventions through providing an outcome measure that can detect differences in trials focusing on unmet needs in multiple myeloma. Symptoms as outcomes could then be used in combination with other outcomes as composites. This was attempted in two studies, one with advanced non-small cell lung cancer patients, combining an improvement in one or more symptoms with a specified improvement in performance status to be defined as a positive clinical response (984,985). Guidance regarding PRO instruments in research states that shorter recall periods are preferred since longer periods of one to four weeks may increase measurement error through recall bias. The MyPOS with its time frame of asking about the previous three days therefore might improve capturing changes in symptoms over time in trials. The two validation studies of the MyPOS have shown that its psychometric features support this use. Information from physical symptoms and emotional functioning items can be aggregated into two unidimensional subscales, as supported by the results from factor analyses and Rasch modelling. Deriving an MID for the MyPOS will aid sample size calculation and valid interpretation of important differences. The

MID makes it possible to report the magnitude of treatment, which constitutes a much more powerful approach than selecting a thresholds arbitrarily or dichotomising data, as often done in the absence of MID information (920).

The MyPOS is a new disease-specific questionnaire. In comparison to the EORTC QLQ-MY20 (221,310), the myeloma-specific QOL questionnaire developed by the EORTC group, the MyPOS has the drawback of not having the same history of use. The generic EORTC QLQ-C30 has a wide-spread application in clinical trials, being used in 75% of RCTs in haematological cancer (986), and representing, together with the MY20, the most commonly used tool in clinical trials in multiple myeloma (359). The EORTC and likewise the FACT group in the United States have had fifty years of facing the challenges of implementing QOL into research, addressing measurement challenges by providing modular assessments of QOL, cultural adaptation of questionnaires, developing guidelines for protocol development with QOL as endpoints, and, most recently, providing guidelines for use of QOL in clinical practice in addition to clinical research (401,987). Rather than suggesting the MyPOS being suitable for all clinical research, it has a specific place in RCTs including the more advanced stages of multiple myeloma, as an additional measure.

Besides this use, other applications in research consist of more descriptive explorations of reasons for treatment non-adherence or discontinuation. Withdrawal or non-adherence is often related to toxicity which can be documented in the MyPOS. Its integration can also serve the purpose of understanding intermediate and ancillary study endpoints or variables. Following the model of QOL (357), the MyPOS contains items representing intermediate and more distal variables impacting on QOL and thus provides the opportunity for modelling these pathways.

8.4.2 The clinical use of MyPOS (screening, assessment, monitoring)

With increasing survival rates in haematology and a greater variety of treatments available for multiple myeloma, questions about long-term effects of treatment and best supportive care emerge for patients. To answer these questions, QOL knowledge and QOL assessment need to be integrated into clinical practice. This is one of the areas in which both parts of this thesis, the further development of the MyPOS as a tool for monitoring QOL in patients with multiple myeloma and the development of a model of predictors for poor QOL. The intention is to provide a framework for clinical evaluation of QOL, for patient education and for deriving interventions to maintain or restore QOL and to focus on those patients who might benefit from palliative care involvement being at high risk of multiple symptoms (93).

Survival prediction models have been largely based on disease characteristics, biochemical variables, and performance status (146). The current study shows that for the outcome poor QOL,

factors with predictive power are not those associated with disease or treatment characteristics but patients' self-reported symptoms and functioning. Patient's self-reported aspects of health status have been demonstrates as useful for estimating survival in cancer patients (166,192,223,241,988-991). The model of predictors could be used as a conceptual model to develop a PRO measurement strategy of when monitoring HRQOL is particularly beneficial for patients. The model also demonstrates the need for proactive symptom management and better symptom control in multiple myeloma (in particular pain, fatigue, breathlessness, emotional problems) early in the course of the disease and in later stages. Screening and supportive care interventions (in particular psychological services) are warranted, as is an awareness among clinicians of the emotional distress and concerns about the future and compromised physical functioning in myeloma patients.

Patient-reported outcomes are characterised by a flexibility that makes them ideal for their repeated application essential for longitudinal monitoring. PROs also provide the patient's view of their functioning and areas of concern. Greenhalgh (2009) (38) in her theoretical framework of the application of PRO in clinical practice, describes four areas of application, depending on two dimensions – the level of data aggregation and whether the application involves data use within the encounter between clinician and patient or not. Among the application of use of PRO data from individual patients, she describes screening, monitoring and – if data is reviewed by a group of clinicians - facilitating communication within multidisciplinary team meetings. Group-level aggregated data, if used in the encounter between clinician and patient, can provide decision aids for patients when considering PRO scores and toxicity profiles before selecting a new treatment or when weighing different treatment options. This application has been studied in breast cancer patients (992-994), but – with more data emerging from clinical trials and even from long-term surveillance data of anti-cancer therapy – could also be applied to multiple myeloma. Decision materials are provided in the form of Patient Decision Aids (430,433), enabling patients to make informed decisions between treatment options, by presenting all options and information in patient information leaflets. The other form is a professional decision support system (995) in which evidence-based choices with incorporation of QOL information are presented to clinicians. Treatment decision making in myeloma would be greatly enhanced by the ability to balance QOL-related impact of treatment with traditional outcomes such as survival time, durability of remission, toxicity of treatment and symptom palliation (85). This can only be achieved by collecting QOL data in clinical practice to aid post-marketing surveillance of treatment benefits (450).

The last quadrant defines PRO use at the population level for assessing quality of care and even deriving PRO-based benchmarks. This approach has been used successfully in elective surgery in the United Kingdom (438) and in palliative care in Australia (442-444). Similarly to Greenhalgh

(2005) (427), Osoba (2002) (996) and Sutherland & Till (1993) (431) define levels of decision making when applying PROs in clinical practice, distinguishing between a micro, a meso and a macro level. The micro level corresponds to Greenhalgh's (427) first quadrant of screening and monitoring of an outcome, the macro level corresponds to the population application. The meso level is the application of PROs in clinical trials which was covered in the previous section. Yet another framework of PRO use in clinical care contrasts cross-sectional with longitudinal applications (997). Cross-sectional applications are assessment, screening and shared decision making, whereas longitudinal applications are symptom management, outcome assessment and quality improvement. For example, the MyPOS can be used to identify the necessity for a formal patient evaluation or supportive care intervention when screening symptom burden and palliative care-related concerns. A similar application relies on tracking symptoms and treatment effects over time and identifying opportunities for improved symptom management or palliative care involvement in myeloma. Longitudinal MyPOS data also is the prerequisite for outcome assessment (448) and quality improvement through audit, service evaluation and benchmarking (316,997).

When considering the clinical applicability of the MyPOS, the initial focus needs to be on its wide-spread use for screening and monitoring. Screening is the one-off application of an assessment instruments to potentially identify troublesome symptoms and problems (664), ultimately leading to interventions to treat the problem and decreasing its severity. Monitoring is the regular, ongoing assessment of the individual patient to check whether a treatment is working or to aid the early detection of disease progression or development of further symptoms (38). The rationale for screening is the detection of problems that would go undetected otherwise (145). The underreporting of symptoms is a phenomenon that has long been described in the literature (998-1000). For example, a study in specialist palliative care estimated the amount of symptoms to be undetected without systematic screening as high as 66% (1001). Disconcordance between physicians and patients results in underestimation of symptom severity in 60% of symptom dimensions. Overestimation of 77% has been described when comparing caregiver and patient ratings (1002). Several reasons for the under-detection and the disconcordance between patient self-report and clinician assessment of symptoms have been proposed. Patients may consider symptoms not severe enough to warrant medical attention or may perceive a symptom as inevitable with no treatment available (703,1001). Clinicians may judge a symptom as uncommon or may feel that they have nothing to offer as treatment and thus not inquire about the presence of certain problems such as fatigue or sexual functioning (1003).

The process of screening is resource-intensive. First, patients need to be made familiar with the tool and the process needs to be explained to them. Staff may be needed to collect the instrument. Above-threshold values must be monitored by clinicians and results must be formatted for

clinicians to be readily interpretable for decision making. Results of PROs such as the MyPOS need to inform treatment decisions – either to stop or modify the current plan of therapy or add supportive care interventions (450). Ideally, assessment should be considered a longitudinal activity. Baseline information could be followed by periodic assessment during and at completion of therapy, at follow-up visits and through treatment-free intervals into later stages of disease (1004). However, this continuity of assessment would require patients being followed through different settings and care providers, something which is not readily achievable in myeloma care. Incorporating MyPOS screening routinely into haematological care could promote a new patient-centredness in health care, seeing PROs not as adjuncts or added tasks to usual care (555). It can be used to identify the most pressing issues that the patient wants help with and such information can guide resource allocation, care planning and patient referrals (1005-1007). This would require PROs like the MyPOS being used to organise health care. Patients would be screened repeatedly when well or sick and not at one point in time as is current practice in the UK with the assessment of supportive care needs (96). Systems could be built in such a way that electronic, web-based screening is combined with feedback and guidance as well as access with information about wider resources like self-help for patients.

Both the model of predictors developed in results chapters 5 and 6 and the development work of the MyPOS may inform what the essential issues are that need to be screened or monitored using PROs. Ideally, screening and monitoring should involve symptoms indicating progression of disease and side effects of treatment, performance status, degree of psychosocial or spiritual distress, personal goals and expectations, information needs and understanding of the disease/concerns about the future (1008). All these aspects, except performance status, are covered by the MyPOS. Especially the presence of symptoms such as pain or fatigue, the general symptom level, Eastern Cooperative Oncology Group performance status of 2 or above and potentially information about disease stage could form screening criteria. For patients who meet these initial criteria, palliative care involvement might be warranted, with additional assessments and review by an advisory palliative care team or other forms of models of palliative care being provided to myeloma patients (267). From the prevalence figures seen in the cross-sectional analysis in chapter 5, screening of sexual well-being and financial difficulties is also important. Sexual concerns and financial issues are two aspects that are readily sidestepped by oncologists in patient consultations (821,822,1008). Forbat and co-authors (2012) (822) found that when sexual functioning was raised by the patient, the oncologists were apt in finding medical explanations which did not result in a discussion of how to manage the emotional side of these issues. Education and training as well as development of resources that patients can access via the internet or through patient charities can help with these two problems in particular (1009). Regarding screening of symptoms, there has been a debate in the literature around the value of a

common set of symptoms versus more targeted screening of specific symptoms indicating risk (510,1010). The MyPOS offers both these options by providing a list of common and frequent symptoms in multiple myeloma, both disease- and treatment-related, with the option of adding additional symptoms that patients find troublesome.

Screening and monitoring in myeloma can learn from approaches that have already been tried in psychosocial care. Information on the trajectory of QOL in multiple myeloma together with the model of predictors could inform risk-targeted assessment at transition points in the disease trajectory. This could be combined with a layered model of screening in stages that is common for distress screening in oncology (360). The National Comprehensive Cancer Network (NCCN) in their guidelines recommend a simple screening tool, the Distress Thermometer (DT), for initial screening of psychological or spiritual distress in cancer (647,1011). A cut-off point is defined to help identify those patients with significant distress. What follows is a staged model of further assessment and management, depending on the level of psychological distress. With mild distress, the NCNN recommends management by the primary care team with information and relaxation exercises being provided to the patient. Moderate to severe distress should involve proactive referral for further assessment and treatment by a mental health professional or social worker. The highest levels of distress need to be evaluated by a psychiatrist (360,647,1011-1013). A similar model of screening/assessment in levels is proposed for symptom assessment in advanced cancer (1014). Level 1 consists of screening of important domains such as common symptoms and cognitive impairment. Level 2 explores more symptom dimensions and mobility. Level 3 involves psychosocial variables and should be combined with daily follow-up and review of physical and psychosocial distress (1014). While this model of screening tries to confine comprehensive screening to the higher stages of distress, it may still be too elaborate for assessing the breadth of symptoms important in multiple myeloma, given that multiple symptom dimensions need to be assessed in level 2 (1014). The model of distress screening proposed by the NCNN better suits the needs of identifying symptoms that are clinically significant and thereby identifying patients that would benefit from further assessment and care (1012,1015). Rather than proposing an initial screening only comprising one question or an abbreviated scale, such as recommended by the NCNN (647) and Kirkova (1014), screening following a multi-symptom approach with a moderate level of detail, as in the MyPOS, might provide a more detailed picture, yet allowing a focus on the most important problems. This study has shown that self-assessment is possible even in those myeloma patients with poor performance status, thus making self-report feasible in this scenario (1016,1017).

As a way to potentially relieve clinical services from resource-intensive regular comprehensive screening as part of the routine care of patients, such evaluation could be targeted to at-risk groups at different points in the disease trajectory when patients are most at risk of developing a poor

outcome (93). Zabora (2015) (360) suggested linking clinical with psychosocial challenges in multiple myeloma and establishing comprehensive screening at these transition points. The authors recommend screening at first diagnosis, even in asymptomatic patients, screening during active treatment, at point of entering remission, during each subsequent relapse and when the refractory stage is reached (93,360). This screening could be combined with information from the predictor models to target those patients with poor performance status in particular. From this longitudinal study and the high prevalence of problems found even in stable phases of myeloma disease, I would like to recommend at least one regular assessment time point during each treatment-free interval or, alternatively, to provide patients with the facility to self-complete the MyPOS with alerts being sent to the clinic. The fact that patients are classified as asymptomatic or stable, according to their disease activity, does not mean that they are not distressed or are experiencing symptoms, a fact that is overlooked when assuming that trajectories of psychosocial concerns follow trajectories of disease activity and severity. Among others, this was shown in a recent study with newly diagnosed multiple myeloma patients in which over 50% of patients expressed preferences for psychosocial interventions at the point of diagnosis (1018). This result has been echoed in studies with HSCT and other cancer populations (1019,1020) as well as in this PhD study.

When thinking about the clinical applicability of the MyPOS in screening and monitoring, screening and monitoring physical symptom burden, caregiving burden and psychosocial distress in informal caregivers needs to be mentioned as well. It is important for clinicians to screen at least for emotional distress and information needs as well as readiness to manage illness-specific problems in caregivers (1021). Offering psychosocial support to family members of patients with multiple myeloma at multiple points in their disease trajectory is recommended by the NICE guidance (96), but it is not explained how such support should be targeted and delivered.

Overall, the questions and problems arising from resource-intensive screening point towards a change in existing models of follow-up care in multiple myeloma. First, the increase in numbers of patients being followed puts pressure on clinics. Face-to-face hospital appointments with intervals between appointments increasing over time is a static model of follow-up. Concerns have been expressed about the effectiveness of this model of care (1022). Second, this model has been shown to be ineffective in detecting recurrence, whereas recent research has demonstrated that symptom screening could detect relapse in lung cancer early (645,646). Third, one argument for clinic-based follow-up is maintaining contact with the clinical care team. However, shorter consultation times result in information and psychosocial needs remaining unmet (1023,1024). Rather than follow-up through primary care or telephone follow-up, eHealth applications of monitoring could be combined with open-access clinics where patients can drop by on demand (475,1025,1026). Electronic patient-monitoring can help the integration of PROs like the MyPOS

in regular assessment of myeloma patients. Web-based systems offer a number of features that allow an easy integration into existing workflows and provide reliable, reproducible and high quality data (411,420,427,432,1027-1032). This prospective use of QOL information would allow remote monitoring with PROs such as MyPOS being completed at home, alarms being sent out to clinics if scores are above-threshold, patients being reviewed by the clinicians if problems arise, indicators and alarms being set according to risk models of QOL in multiple myeloma and clinicians being provided with immediate scoring results for the patients, allowing subsequent further diagnostic assessments (1033). Such an integrated system could offer further features. Next to its primary purpose, providing a measurement feedback system to patients and clinicians with multiple outcome scores, such a system could have built-in personalised advice and reference to supportive care services (1034). In this way, the multi-step model of distress screening and management could be incorporated into an eHealth application for QOL, by providing the first or lowest step on the ladder in the form of additional information, links to web-based help and guidance as those offered by patient-led charities like Myeloma UK or the NHS, and even offer specific self-help interventions (i.e. relaxation exercises) (1034-1036).

Several systems of electronic PRO data collection have been tested over recent years (189,453,473). The first and most prominent system was developed at the Memorial Sloan Kettering Cancer Center to monitor adverse events during chemotherapy in advanced cancer patients (42,404). The most recent RCT, published in 2016, used electronic PRO collection by sending weekly e-mail prompts to patients between visits. Physicians were made available symptom profiles during the consultation and nurses received e-mail alerts when scores indicated severe or worsening symptoms. The trial showed a HRQOL benefit in the intervention group, together with less frequent admissions to the emergency room or the hospital and longer time of patients on chemotherapy (43). This system mainly focused on chemotherapy-related toxicities. Similar systems have been built for monitoring other patient groups, i.e. general health (1037), child behaviour and development (1038,1039), general oncology (455,586,1040), and the general outpatient setting (42,463,469,1037,1041). Within palliative care, a few initiatives have centred on developing a core set of measures for monitoring palliative care patients. Amy Abernethy has developed an electronic system, the Patient Care Monitor (1042), to address under-identification of symptoms and distress in oncology clinics. An Australian initiative has built a system to monitor rural palliative care patients via the telephone (460,462). The only system that could be located using tracking of symptoms and mental health in hospice patients was a system using web-based reporting from home in hospice at home patients (465). In Canada, a national system using repeated assessments of ESAS symptom scores improved predictions of death in cancer patients (990). A new study using electronic patient-reported outcomes for monitoring in the UK links electronic and data collection via mail with cancer registries (470).

Most of these projects have not been evaluated in RCTs. Exceptions are the study by Basch et al. (2016) (43) and a study in HSCT patients testing a system of PRO collection with results being provided in form of a graphical summary to clinicians before the patient's clinic visit (467). Also, some of these systems do not provide a fully-integrated workflow with some still requiring manual PRO collection. Integration of clinical data into PRO reports is seldom achieved. Another key difference between systems is the feedback loop. Some provide PRO data to patients and clinicians, some only provide the clinician with the PRO information the patient has entered (473). Systems most widely differ in the incorporation of educational materials and giving guidance and promoting self-help in patients for addressing symptoms outside clinical interactions. This feature, one of the main benefits of electronic monitoring and easily achievable, is the one that is used least often (1043-1045). These aspects should be built into a system of using the MyPOS for electronic monitoring. The MyPOS offers some features that are desirable in this context, namely the potential for personalisation by adding additional symptoms to the scale. The identification of main problems and concerns at the beginning of the measure offers an opportunity for further personalisation and for tailoring information and guidance to the individual patient. At the same time it has been shown in the psychometric analysis that the MyPOS is robust and sensitive enough to detect changes over time to be used for monitoring, with the potential to define cut-off values for alerts to clinics that the patient needs to be reviewed by the clinical team, thus allowing a new model of follow-up care (1046).

Lastly, I would like to focus on one potential feature that an electronic patient-reported outcome system could offer. This addresses a gap often cited as a barrier to clinicians using PROs in clinical practice (40,400,1047,1048) - the paucity of linking assessment to suggested action by providing guidelines of PRO-linked interventions (40,90,1049). Only one group so far has incorporated guidelines for treatment and intervention of QOL-related problems into their system, the Patient Viewpoint (1048). When viewing patient results, doctors or nurses can click on a link labelled "What can I do" that takes them to recommendations emphasising the need for further assessment and evaluation, as well as pharmacological treatments and referrals to other members of the multi-disciplinary team (1048). The authors provide consensus recommendations for eight symptoms, two psychosocial issues, problems with various aspects of functioning including sexual function, overall QOL and information needs. Some of these recommendations could be transferred to myeloma-related problems, some recommendations regarding issues particular to this disease group would need to be developed for an electronic PRO collection system of the MyPOS. Since the MyPOS is a module of the Palliative care Outcome Scale, some recommendations could be taken from the set of guidelines produced for five common problems as seen on the POS (1050). This would result in a fully integrated system, a streamlined

application of regular assessment, patient-empowering information provision and guidance a well as recommendations for actions linked to identified QOL-related problems.

8.4.3 Recommendations for the integration of haematology and early palliative care involvement in the care of multiple myeloma

Assessment in form of screening and monitoring and, in particular, the use of the MyPOS for such a purpose can also aid the better integration of palliative care into general haematological care of patients with multiple myeloma. This view is supported by recent guidelines published by the NCCN in America (647,1051,1052) and the slightly older NICE guidance for the UK (96). These guidelines call for routine screening and early intervention at regular intervals with re-assessment indicated by an overall change in function. They further recommend the integration of palliative care into the general care for haematological cancer patients, even those undergoing treatment, if they meet screening criteria (647,1052,1053). However, one should note that despite targets for palliative care screening being the same as those in oncology, in palliative care symptom management is not pursued with the explicit purpose of allowing more active cancer treatment. It rather serves the identification of needs and concerns that will help in alleviating symptoms and optimising QOL (1008).

This study has demonstrated the high prevalence of symptoms in a sample of multiple myeloma patients at different stages of disease. Fatigue, pain and breathlessness were the symptoms with the highest prevalence of 88, 72 and 61%, respectively. Other problems, particularly anxiety, depression and worry about worsening of the disease, were as common. This highlights the problem described in the literature for almost all haematological disease patients and HSCT populations, namely the generally high and complex symptoms that persist even in treatment-free intervals (83,593,734,1054) and the challenge this poses for continued care. By contrast to many other haematological malignancies, myeloma has many potential complications including bone disease and the severe and complex pain resulting from it, a generally high level of comorbid disease due to the advanced age of patients and disease complications such as renal failure (1051). Moreover, myeloma displays features of some non-cancer conditions with a prolonged illness trajectory extending years due to the introduction of novel agents, also resulting in accumulation and multiplicity of treatment- and comorbidity-related toxicities and other health problems (706). Such pathways are now associated with long-term follow-up which can result in interruptions in the continuity of care and patients expressing unmet needs for supportive care and symptom control (90). Lack of continuity of care is especially problematic at the end of first-line treatment at which point patients leave tertiary care and are followed-up in the community (90).

The symptom burden of haemato-oncological patients has been shown to be comparable to those with advanced solid tumours (93,234,1015). However, the pattern of symptom prevalence and their severity can be different which has implications for the model of care (93). Some new care models including wider supportive care have been proposed in recent years to address the high amount of unmet needs experienced by HSCT and haematological cancer patients throughout the disease trajectory (88). These survivorship care plans contain schedules for follow-up and review in clinics, review of symptoms and treatment-related toxicities, supportive care as in blood product support or maintenance chemotherapy and psychosocial and nutritional support, if needed (998). Several different models of monitoring patients in cancer survivorship care have been described and tested, some instituting specialist and multi-disciplinary or oncology-led outpatient clinics (1055-1060), some proposing models integrated in primary care or collaborative models between primary and specialist care by sharing specialist nurses with primary care practices (474,1055,1058-1062). However, high-quality evidence regarding the effectiveness of these models of follow-up care is still lacking (998). On the one hand, survivorship care includes the components of coordination of care, monitoring, prevention and screening as well as psychosocial support and information provision that are needed to address the unmet needs of patients with multiple myeloma (90,385,482). On the other hand, despite myeloma patients formally falling within the definition of survivors when living beyond five years with their disease (477), the incurable nature of their disease makes the use of the language of survivorship difficult. This could foster wrong hope in patients with myeloma.

However, one aspect from survivorship models could be implemented in routine myeloma follow-up. This is the use of multi-disciplinary teams that manage the multi-dimensional symptoms and concerns of patients (477). This and other studies showing a spectrum of QOL-related problems (381,593,803) highlight the range of resources that are needed to offer comprehensive care with an ongoing multidisciplinary approach (593). Multi-disciplinary team (MDT) meetings have been the preferred model of care in complex and chronic conditions for many years (434). However, MDTs in oncology care are different. They usually consist of a different mix of professions than is common in chronic conditions or palliative care. MDTs in cancer specifically deal with only one type of cancer, often including specialists for diagnosis like radiologists and histopathologists. Their organisation and composition is left to local discretion and regular review is the exception with many patients being discussed only when first entering the service or at point of diagnosis (1063). These MDTs focus on diagnosis and curative treatment rather than the minimisation and optimal management of symptoms throughout the cancer pathway (434). Consequently, there has been little empirical support for their effectiveness (1063,1064). However, truly multi-professional and inter-disciplinary team meetings could offer a way to address the need for complex and comprehensive long-term care in multiple myeloma and other haematological cancer

patients, by using PROs such as the MyPOS to detect and screen for areas of concern and discuss a care approach to address these areas of unmet need. This would require a restructuring of team meetings and changing the attitude towards these MDTs, the inclusion of nurse specialists and the wider psychosocial team within facilities, possibly also comprising specialists for non-pharmacological treatment of symptoms in myeloma such as physiotherapists and occupational therapists (1015,1040,1065).

Evidence that haematological cancer patients receive less specialist palliative care in hospitals and referral to home care or hospice services has been accumulating for some time (137,152,158,159,706,1066). A large gap exists in the access to palliative care for multiple myeloma. Different barriers to the integration of both specialities have been proposed at the level of the patient, the illness, clinicians and the health care system (140). Among reasons pertaining to the system are the level of generalist palliative care skills and funding shortages of integrated models (694). Clinician-led barriers centre on attitudes and the reluctance or inability to define the palliative status and predict the time to death in this patient group (93,105,130,158,162,261,264,1066,1067). Given that there is no commonly agreed definition of a palliative care patient (1068), their might be disagreement about the suitability of myeloma patients for palliative care. The disease trajectory of multiple myeloma also makes it impossible to reliably predict survival early on and deterioration can happen quickly. As such, myeloma resembles trajectories of non-malignant disease which are characterised as having entry-reentry patterns with frequent hospitalisation, exacerbations of disease resulting in declining functional status but intermittent stabilisation phases (694). Also, multiple myeloma patients are usually burdened by two or more comorbid diseases, which may add cumulatively to their under-representation in specialist end-of-life (EOL) care (1069,1070). Attitudinal barriers in clinicians can go hand in hand with attitudinal barriers in patients. On the one hand, in the few studies examining advance care planning in the HSCT and haematological population (132,1071), it has been shown that most patients want honest information regarding the risk of death when obtaining information about the benefits and harms of chemotherapy (132). On the other hand, the sickest patients with the highest chance of dying were the least likely to perceive their poor prognosis. Referral to palliative care services has been described by some patients as leading to the feeling of being abandoned by their clinical team (138,162). Haematologists may feel that a referral to palliative care indicates that treatment is no longer aimed at curing and causing a sense of hopelessness in the patient (132,160).

Therefore, unique care models might be needed for the integration of palliative care into general haematological oncology (160,1072). There are different templates of integration, particularly for early involvement of palliative care, some of which have been tested in the stem-cell transplantation setting (161,263,1073,1074). A link between the two specialties would greatly

benefit patients and staff. Haematological clinical staff needs to be skilled up in generalist palliative care provision and palliative care specialists are in need for training in the unique issues faced by haematological cancer patients (261).

To foster the integration of palliative care with haematological care, it helps to distinguish between generalist palliative care and specialty palliative care (1075). This distinction is akin to the model of levels of distress management proposed by the NCCN (647), whereby different levels of need are met by different and more extensive skill-sets in the professionals (1075,1076). Generalist palliative care comprises basic symptom management of physical and psychological symptoms, communication regarding cancer prognosis and goals of treatment as well as advance care planning (1075). Specialist palliative care (SPC), however, is reserved for complex or refractory symptoms, communication issues and conflict management between patients, family members and healthcare professionals. While this model recognises that oncological teams can deliver palliative care – given that they receive specific training by palliative care specialists – it also recognises the fact that SPC involvement has its place not just at the end of life in haematological care, but potentially earlier on. This would require a paradigm shift in the perception of oncologists about the adequate timing of palliative care. Currently, a prognosis/survival model dictates when referrals to SPC are made (151), which disregards the needs-based approach that Quill and Abernethy (2013) have proposed in their model of generalist/specialist palliative care provision (1075).

Overall, referral to palliative care is highly heterogeneous. This situation is not helped by the absence of palliative care in treatment guidelines of multiple myeloma and other haematological cancers (1077). Palliative care was only mentioned twice in the latest National Comprehensive Cancer Network guidelines for multiple myeloma and non-Hodgkin lymphoma and not at all in the guidelines for Hodgkin lymphoma and several types of leukemia (96). The situation in the UK is different, possibly aided by guidelines for supportive care which are symptom-focused and encompass end of life care as well recommendations towards multidisciplinary collaboration with specialists in palliative medicine and appropriate interdisciplinary referral (126). This might result in the higher rate of specialist palliative care referrals seen in myeloma patients in the UK (137). Hui et al. (2015) (265) have suggested rebranding the term palliative care into supportive care which they advise might overcome the stigma associated with this discipline. However, given that supportive care is in itself a technical term within myeloma care, usually comprising pain management, management of bone disease, fatigue, anaemia, infectious complications and nutritional and psychologic support during therapy to enable patients the completion of their chemotherapeutical regime (87-89,701), rebranding does not seem to be a solution to this problem. Rather, thinking about models of care, clinical pathways and bringing a health services/population perspective to haematological care could help overcome attitudinal and other

barriers regarding the integration of palliative care. A few successful examples of pilot projects exist. In response to the high prevalence of invasive medical interventions at the end of life in haematological cancer patients and the high incidence of hospital deaths in this group, comprehensive programmes based on multidisciplinary home care services coordinated with haematological wards and hospices, have shown to have had an impact on patient and family satisfaction and the time spent in hospital in the last days of life (501,1072,1078-1082). An Italian initiative has worked to develop integrated care plans including care pathways for terminally ill and dying patients and enabling home care both for patients undergoing high-intensity treatment as well as palliative patients (1072).

These examples demonstrate that an integration of the principles of palliative care with haematological care is possible. For more patients of this neglected group getting access to the speciality, I suggest two changes to the current practice: defining new risk models for identification of suitable patients, thereby moving from survival prediction at time of diagnosis to a monitoring approach, and early, temporary integration of palliative care instead of a sequential model of haematological and end of life care. Current routine monitoring and prognostic risk stratification comprises a considerable number of clinical and laboratory findings, among them biomarkers for disease staging and chromosomal abnormalities, which carry prognostic information for survival (806,1083,1084). Many of these prognostic tools are scored at diagnosis, but less so after disease progression (139). With every treatment cycle and line of treatment, response to treatment, measured by changes in the Myeloma-protein component level, is evaluated (1085). However, M-protein level is a surrogate marker with considerable measurement error (26,205), its evaluation is confined to end of treatment/routine follow-up and its usefulness for indicating the need of palliative care involvement is limited (139,230). In recent years, answers to the questions of prognostication and suitable indicators for the need of palliative care have been developed, particularly for non-cancer conditions in which prognostication and the definition of a palliative care patient are equally contested and difficult (694). These indicators centre very much on performance status, sometimes combined with other signs and symptoms. Among them, the most widely used are (202): the Palliative Prognostic index (204,812,1086-1090), combining performance status with oral intake, oedema, breathlessness at rest and delirium, the Charlson Comorbidity Index (195-200), deriving risk of mortality from a weighted score of comorbidities, and the Glasgow prognostic index (1091), combining serum CRP and albumin levels into an inflammation-based prognostic score (thus it is often used in the chemotherapy setting). One recent study from the National Hospice Organization has found that Karnofsky Performance Status together with the presence of five symptoms indicated a median survival of 6 weeks (1092), although a change in performance status that is not reversible has been shown to be an equally potent indicator for palliative care involvement in cancer patients

(1092-1097). The problem with this array of possible indices is their focus on the end of life. Their aim is to identify patients with a survival of 3 months or less (202). They have only been validated in palliative care populations and thus have limited generalisability to other settings. Given that some patients with myeloma show compromised general mobility early on in their disease trajectory, caused by spinal lesions and myeloma bone disease, performance status may be of limited usefulness for prognostication (47,87,90,92,379,499,598,701,750).

There is a call for prognostic models that integrate biological and patient-related aspects, in particular joint predictive models of biomarkers and longitudinal PRO data (1098). This recognition of complexity and the need to honour the patient perspective stems from evidence that has accumulated over the past 20 years. It has been shown that symptoms and aspects of QOL carry prognostic significance for survival that often exceed the strength of association of clinical biomarkers (229). Among the symptoms, fatigue and drowsiness are emerging as main factors, being associated with survival in over 50% of studies (16,225-229,767). This has been found for solid cancer patients (223,238-240,1099,1100) as well as haematological disease patients (164,241,810,1101). In our systematic review, we likewise found a higher absolute association of symptoms and patient-reported outcomes than for biomarkers or demographic factors. Tracking aspects of QOL over time therefore has the potential to provide a more relevant way of identifying who might benefit from palliative care in multiple myeloma. From a clinical perspective, the results from this study suggest that patients with poor performance status, high symptom burden and the presence of fatigue or pain could be considered as potentially benefit from palliative care programs. These aspects could be monitored using above-threshold values of the MyPOS.

To meet the demand for palliative care in haematology, new models of co-management and early integration need to be developed. Evidence for the feasibility and effectiveness of early integration has been emerging in recent years for solid tumours. Three RCTs have tested different models of outpatient early palliative care and showing effects on a number of physical and psychological symptoms, QOL and even prolonged survival of metastatic lung cancer patients (172-174,277). Less stringent evidence from retrospective and prospective cohort studies investigated different models of outpatient collaborative oncology and palliative care (1102-1104). One also needs to bear in mind that the existing few studies had considerable variability in setting (i.e. stand-alone clinic versus integrated clinics versus home-based palliative care provision), timing (upon referral or simultaneous care), and the number and types of interventions within palliative care that were delivered (1102-1104). It is currently unknown which model of integration works best. None of these studies included haematological cancer patients, therefore the transferability of this model needs to be researched. Only two retrospective studies including leukemia patients could be located that tried a collaborative model of care between

haematological cancer care and the palliative sector (143,153). Preliminary effects shown were symptom alleviation, advance care planning, home care provision and hospice referrals and bereavement care for family members (143,153).

Currently, the predominant model of care is the "solo practice" model as defined by Bruera and Hui (2010) (248). In this model, palliative care provision is completely separate from oncological care and the haematological team provides all disease management and supportive/palliative care. The first level of integration exists when interdisciplinary care is provided by referral to supportive and palliative care services as needed. However, the main responsibility remains with the haematologists, referral to palliative care happens too late (1105) and results in patients being seen only at the end of life. The lack of interaction among the different specialists can result in adverse events for the patient (248). The step to a fully integrated model between primary specialist and palliative care team is taken when multidisciplinary team meetings are held with palliative care consultants present and seen as full members of the primary care team (248). Different approaches to achieving this level of integration range from embedded clinics (277,1106), to outpatient palliative care clinics within oncology (172,174,1107,1108), inpatient palliative care advisory teams (1109), and combined patient care rounds or MDT meetings (1106)

To routinely involve palliative care, ongoing communication between the specialties is needed (162). Universal screening criteria both for inpatient and outpatient settings (178,1110) could help identify patients earlier on in the disease trajectory. At a minimum, standardised assessment of palliative care needs and concerns is needed, for example using the MyPOS or similar tools, to accomplish the management and treatment of the identified symptoms and problems (275,277,1111). This would require addressing the attitudinal barriers and provide training to foster haematologist's willingness to base their treatment decisions on patient's QOL and be open to such co-management models (515). If early integration is achieved, potential effects would be the reduction in patients with multiple myeloma seen too late in their disease strategy. Also, early involvement could lessen the stigma of equating palliative care with end of life care (1112). Instead, patients and their families could develop a longstanding relationship with the palliative care team, similar to the trust they develop to their haematological care team (277). Developing this therapeutic collaboration can prepare the ground for difficult conversations regarding advance care planning, weighing the benefits and harms of treatment options and achieving clarity regarding the patient's goals (277) Some authors also see the major benefit of early palliative care referral in the psychosocial support provided even to newly diagnosed patients (153).

8.4.4 Training, resource and policy implications

Significant barriers still prevent the early integration of palliative care into the continuum of haematological cancer care. Some of these include the lack of payment models to support a co-management model (1112). Others are the considerable lack of trained professionals (277). Treatment and the profile of side effects are complex in haematology and the special needs of haematological cancer patients at the end of life regarding management of infections and bleeding have been listed as barriers to integration (151,153,707,1113,1114). In an integrated and interdisciplinary model of care, haematologists and palliative care could learn from each other, both regarding aspects of tumour biology and anticancer treatment and knowledge about management of complex symptoms and psycho-spiritual care (154). This would involve broadening oncology training to communication skills programs (1115) and allowing rotation of registrars across the disciplines.

Tied into this aspect is the general training of the workforce that is needed to fully implement patient-reported outcome measures in clinical practice. Among the systematic reviews on PROs, none covers the process of implementation of outcome measures into clinical practice (37,417-423,966). But if PROs like the MyPOS or others are envisioned to guide care and be used for routine screening and monitoring of patients in oncological practice, an implementation strategy is needed to change processes of care. Implementing PROs into routine practice is an issue of the organisation rather than the individual. Several systematic reviews of qualitative research have highlighted barriers to routine use that need to be addressed (37,417-423,966). These stress the need for a set of implementation strategies covering education, audit and management of change within the organisation. Such an implementation also requires resources at the outset, clinician input into the system, and planning feedback that patients and clinicians receive from the system, the format and the additional time that data collection and documentation will take (453,1116). Grol (1997) (1117) proposed a model for implementing changes comprising the elements (a) educational – sustainable training provided to a changing workforce, (b) epidemiological – provision of evidence-based guidelines of how to react to uncovered problems through screening, and (c) marketing – designing the system involving all stakeholders, but patients and their families in particular. Some of the international organisation, for example the International Society for Quality of Life Research (ISOQOL), have recognised the need for routine implementation of PROs and provided guidelines for their implementation (400). They also stress the need for a high-facilitation model of implementation since PRO use in clinical practice is resource-intensive.

This points towards the fact that changing care and aiding the integration of palliative care into haematological practice requires a population perspective. As shown above, effective

dissemination relies on new information infrastructures and technologies and the redesign of care and thus should not be left to individual organisations. There are several examples of nationwide initiatives that promoted an integrated system of introducing PROs into clinical practice, offering consistent training and facilitation, and using data to inform patient care and/or provide benchmarks and metrics for overall performance of services. The most prominent of these examples is the Palliative Care Outcomes Initiative in Australia (422-424), running as a national program that utilises PROs in palliative care. A similar but less sophisticated system exists since 2007 in Ontario, Canada (1118). All cancer centres including homecare services systematically collect data on performance status and the Edmonton Symptom Assessment Scale in outpatients with cancer. Contrary to the Australian initiative, this system contains province-wide information on general oncological cancer outpatients and thus focuses on patients further upstream. Yet a different way is followed in England. The UK PROMs programme introduced a generic health status assessment via the EQ-5D into elective surgery (438). Rather than directly benefitting patients by developing programmes of how to improve PROs of patients and promote quality improvement of providers, the system relies solely on benchmarks with the aim to provide data regarding which services perform best, so that consumers can select the best quality (442,443,1119).

All these systems envision change by following a top-down approach of changing health care by changing processes. A different model of introducing routine monitoring into myeloma care could follow the approach of putting monitoring into the hands of the patient. Such an approach is gradually being developed by Myeloma UK, a patient-led charity operating in Scotland and England. They have recently developed an online platform onto which patients log on to track their treatments and progression of their disease. Currently this system does not contain PRO information. During a conference held at the Cicely Saunders Institute in March 2016, this subject was discussed with Myeloma UK representatives, service users and clinicians from both haematology and palliative care. The introduction of PROs and promotion of patient-led monitoring could provide a bottom-up approach to the implementation of PROs. However, it should be borne in mind that such a system needs to fulfil considerable security requirements, as every electronic patient record does, and guidelines for clinicians on how to react to certain QOL problems, based on evidence, are still needed.

A third approach, next to performance measurement and patient-led monitoring, could be the coupling of PROs with nationwide cancer registries. This approach has been used in the Netherlands (1120) in the Eindhoven Cancer Registry, which compiles data of all individuals newly diagnosed with cancer in the Netherlands. The EORTC QLQ-C30 is collected routinely on these patients and they are followed into survivorship or until death. The generic QOL module is supplemented with disease-specific or domain-specific questionnaires, i.e. satisfaction with

information provision (1121). There have been numerous outputs from this cancer registry-based monitoring, also focusing on or involving multiple myeloma (381,503,805,1120-1122). Its strength relies on flexibility of data collection, which is either achieved by using a web-based system or via postal surveys. The general population is also surveyed at regular intervals to provide the facility of comparing to population norms. Through the registry, a direct link to clinical data is possible. This data can then be used to identify patients at high risk for poor physical and mental health as well as enabling the analysis of mechanisms leading to specific outcomes (1120). In the United Kingdom, a cancer registry specifically focusing on haemato-oncological patients has formed surveying the population of newly diagnosed haematological patients in two adjacent UK Cancer networks (145). So far, this group yet needs to integrate PRO data. Their current emphasis is on haemato-pathology laboratory parameters, prognostic factors, treatment and response to treatment history and socio-demographic details. This registry has taken efforts of setting up the infrastructure necessary to support monitoring and it would be interesting to see whether they can incorporate the PRO perspective in population-based monitoring.

Following the monitoring idea and the nationwide initiatives to promote patient outcome measures that recent health policy has promoted, the MyPOS could be used in such a system to measure quality indicators of haematological care, but also to indicate the state of integration between the disciplines of palliative care and general oncological care. The number of potential stakeholders has broadened in recent years to not only include policy makers, regulators and physicians, but also patients and their representatives. Their views on the effects of treatment should be included, particularly when health care is predominantly concerned with the treatment of chronic or palliative conditions where improving life quality rather than cure is the aim (435). Both sides, health care and service commissioners as well as patient representatives have called for including outcome measures into metrics, to provide information about the quality of services (439). The availability of such metrics, such as the quality indicators utilised in the Australian Palliative Care Outcomes Collaborative, would allow policy makers to set goals for the quality of healthcare provision, and patients and referring physicians to recognise services with good care provision. Avedis Donabedian in 1966 (448,829) split the elements of quality into the three parameters structure, process and outcome. Outcome is defined as “a change in the health status that can be attributed to preceeding health care” (p. 167). While structure and process variables, such as the presence of a palliative care advisory teams or the numbers of times a palliative care physician or nurse has seen a patient with multiple myeloma, are useful in describing prerequisites to quality, only outcomes can capture this quality. Hence, outcome measures like the MyPOS can be used to capture aspects of quality and, if routinely implemented, could help compare the quality of haematological services in meeting the needs of haematological cancer patients. Current indicators of the integration of palliative care with general oncology still focus mainly on

structure and process variables. For example, presence of in- and outpatient services (structure) and routine screening and documentation of palliative care needs in patients' notes (process) are used (1123). However, for quality to be judged outcomes over time need to be assessed. Possible benchmarks could include reduction in high symptom levels or congruence of preferred and achieved place of death in haematological cancer patients (275,1106,1112,1123). Other benchmarks could include staying symptom-free and thus focusing healthcare professionals on the prevention of symptoms and problems (442,443). Overall, for these metrics to reflect patient experience, outcome measures need to be integrated routinely into health care.

8.5 Areas for future research

This study highlighted the course of palliative care-related concerns in multiple myeloma, and, for the first time, described the longitudinal symptom burden using new statistical and psychometric approaches. The integration of methodological aspects of assessing and measuring quality of life with screening for palliative care-related problems suggests a number of further areas for research regarding both the further development of the MyPOS and using the measure in clinical practice.

8.5.1 Further development of the MyPOS

The psychometric analysis of the MyPOS, both within a classical test theory and a Rasch analysis framework, supported the overall validity and reliability of the tool. However, problems with floor effects, suboptimal targeting and scaling (disordered response categories) were observed. In order to support the utility of the questionnaire in longitudinal applications and clinical trials, these shortcomings should be addressed by revising the scale. Since its initial validation, the MyPOS has been converted partially to fit the format of the Palliative Care Outcome Scale (512), a tool that has undergone several revisions to its scaling, the most recent one during cognitive interview testing prior to forming the Integrated Palliative Care Outcome Scale (IPOS) (818,819). Although this modularised approach addresses some of the challenges facing questionnaires, particularly the aspect of standardisation, it resulted in disregarding the participants' preference of an evaluative response scale that they indicated during the cognitive interviews in the development phase of the MyPOS. Further exploration of the floor effects could entail testing the MyPOS in a larger sample of inpatients and patients at the end of life as well as in patients with pre-stages of myeloma or newly diagnosed myeloma patients in the watch-and-wait group (360). The former two groups are likely experiencing a higher symptom burden than participants in the present study. The latter group might represent a group with low disease and treatment-related symptom burden. This would allow an exploration of whether the MyPOS validly reflects quality

of life concerns at the extremes of its scale. During this exploration, further study of the issue of recall and timing would allow addressing the combination of stable and fluctuating or state-and trait-like items in one questionnaire. Since participants in the longitudinal survey as well as in the piloting interviews voiced concerns regarding the time frame of the questions, different recall periods could be studied and contrasted against each other. This has been successfully implemented for fatigue, for which an equivalence of a seven-day to a four-week time frame has been demonstrated (437) by the absence of differential item functioning within Rasch analysis. However, the study of equivalence and impact of different time frames is one of the largest measurement challenges in PROs and QOL tools. Stull et al. (2009) (870) have provided a heuristic model for selecting recall periods for symptoms, psychological states, global life satisfaction and psychological traits which could act as a conceptual framework for the MyPOS.

Given the higher incidence of multiple myeloma in people with African descent, its cultural adaptation and accurate translation into different languages would aid its utility both in the United Kingdom as well as worldwide. The EORTC and FACT working groups faced a similar challenge, and provided translation guidelines for their tools (1124,1125). Similarly, since the spectrum of multiple myeloma reaches from indolent forms to advanced and relapsed disease, and the application of the MyPOS measure is particularly recommended in a palliative care population, proxy or caregiver versions of the tool should be developed. Both the original POS and the newly developed IPOS have staff-rated and caregiver-rated versions available. Therefore, the development and validation work would be minimal, with approximately 10 patients for cognitive interviews and small samples for validity and reliability testing (869). Proxy versions address the difficulty of collecting outcomes data from physically compromised patients and support the monitoring of the whole spectrum of disease severity. However, although caregiver and patients can be close in assessment, there are known inaccuracies such as over- and underestimation of the severity of physical and psychological symptoms (1126), as demonstrated for the symptom drowsiness in the IPOS (819).

One of the main barriers to the use of PROs in clinical practice is the lack of demonstration of their responsiveness to change and indicating what constitutes a clinically important change on the scale (323,1127). Establishing an MID for the MyPOS, both the total score and its subscales, will also foster the use of the MyPOS in clinical trials. However, as this is the first study to establish the minimal important change for a measure of the POS family, the MID estimates need to be validated in larger studies. Triangulation, the use of multiple methods to determine the MID, is recommended, typically yielding a range of values which need to be narrowed (1128-1130). We tried to follow this approach by providing both anchor-derived and distribution-derived MIDs for the MyPOS. Further research should focus on the problems with the global change rating scale that was used as the anchor in the present study. For instance, violation of the monotonicity

assumption in form of patients reporting they were better on the global change question but reporting a rise in their total MyPOS score needs to be understood and addressed. Furthermore, uncertainty exists regarding the comparability of MIDs derived from observational studies versus those established in clinical trials (1128). It is known that the MID can vary according to the impact of interventions and sample characteristics (1131). A larger database can address its generalisability. This will be harder to establish for the MyPOS as it is for larger QOL consortia like the EORTC and the FACIT group who can integrate data from over 10,000 patients collected in RCTs (1132). However, should it be possible to use the MyPOS as an instrument for routine monitoring of QOL issues in haematology clinics, the resulting large dataset might provide a source for such an analysis. Further validation of the MID should make use of the new psychometric methods to compute change on the standardised latent construct scale (1133). Since Rasch modelling allows the construction of a measure that is both free of influences from the sample and the scale (662,968,1134), its application for establishing MIDs is particularly promising and can yield generally applicable MIDs. IRT analysis can also be used to first evaluate the validity of the global change/transition question used as an anchor in responsiveness analyses (323). This was recently employed in a responsiveness analysis of the FACT-G (323). The use of Rasch modelling/IRT also plays a role in understanding response shift, one of the measurement errors that beset longitudinal studies of PROs (918). Differential item functioning analysis can reveal changes in patients' standards and definitions of QOL and Rasch scaling analysis can help understand the change in the relative importance of domains as patients adapt to changing long-term experiences (918). Methods have been proposed for using the new psychometric methods to study response shift and adaptation processes (728).

An integration of the above mentioned proposed adaptations of the MyPOS – establishing a proxy version, cultural adaptation, using the MyPOS for monitoring and establishing a large database to study its longitudinal validity – could be achieved by converting the MyPOS and its core measure IPOS into a multi-level PRO item bank. An item bank constitutes a hierarchical collection of calibrated and standardised items that provide an operational definition of a latent construct (i.e. quality of life). An item bank therefore covers all relevant domains and all relevant severity levels of this construct. It provides a basis for designing the best set of questions for a particular application and therefore makes possible the derivation of short forms or the dynamic selection of targeted questions based on the characteristics of the patients (i.e. disease severity, study or assessment aim) (1135). The latter can be accomplished by developing a computer-adaptive test (CAT) based on the item bank, a procedure in which the computer determines the next most informative question based on the prior responses of the patient and the respondent's latent trait level that is revealed in these responses (1136). Item banks and CAT are envisioned to be the future of assessment and screening (1137), as they allow to measure with greater precision by

means of shorter questionnaires (345,1116). Both the EORTC and the US National Institute of Health have developed or are currently developing item banks across diseases, either − such as in the case of the EORTC – converting their established standard EORTC core questionnaire into an item bank, or building one as is the case with the Patient-Reported Outcomes Measurement System (PROMIS) (397,398,520,1031). Particularly the PROMIS system makes use of the feature of Rasch analysis and IRT to provide equivalent scores for different instruments and establishing the validity of single items instead of complete questionnaires. This makes it possible to compare QOL results across samples and studies (661) and tailor content, yet using standardised scores (997,1138). It is even possible to customise item banks further, as evidenced by a computerised pilot version of the Schedule for the Evaluation of Individual Quality of Life (SEIQOL) (1139), one of the individualised QOL measures.

Establishing a POS/MyPOS item bank would benefit the routine collection and utilisation of these PRO data in clinical data and bridge the gap to its clinical utility. Chang (2007) (1135) has proposed the introduction of item banks and CAT as aspects of an integrated clinical decision support system for PROs, also consisting of clinical practice guidelines and predictive models based on large databases. The strategy for developing an item bank should follow the general item bank development approach as followed by PROMIS and the EORTC, including literature searches and conceptualisation, formulation of new items/operationalisation, expert and patient evaluations in Delphi studies, field-testing and cognitive testing of items, and lastly psychometric analyses and item calibration (397,398,410). This would establish the first item bank built to support palliative clinical practice.

8.5.2 Validation of the risk model and further observational research

Assessment and measurement of QOL in clinical practice ideally help identify those patients at risk of developing a poor outcome. In this study, the focus was on developing a multivariable prognostic model. In two regression analyses, important factors and predictors were identified. Although development occurred in two stages, first in the secondary analysis of a cross-sectional sample of myeloma patients and then in the longitudinal survey, relative weights of each predictor and a full validation of the model's predictive performance (i.e. calibration and discrimination) in new participants is yet to be achieved. Moons, Altman and colleagues (1140) propose a three-stage process for the validation of risk models. Development, in addition to establishing predictors, entails assigning relative weights to each predictor, optimising the model and correcting for overfitting (635). Validation studies should occur in mostly broad samples of new participants from various institutions to test the model's predictive performance (calibration and discrimination, i.e. does the model correctly identify those at risk and correctly reject those not at

risk) (14,629). The last stage consists of impact studies, in which the clinical utility of the prognostic model for decision making is studied (14). Validation should be done on different and larger datasets than those used for developing the model (629,1141).

For the MyPOS and the proposed classes of QOL experience, this should be done focusing on a sample which is followed up for a longer period than eight months, also to allow the combination of PRO and survival data in this cohort. This would necessitate solving the challenge of recruiting more ill patients, particularly inpatients, stem cell transplant patients and those hospitalised with advanced and relapsed/refractory myeloma disease. This would allow collecting data from subjects that are palliative rather than only from survivors or relatively well, stable patients (95). It can also proof difficult to reach subjects who do not usually respond to QOL survey, but may have poorer QOL outcomes or are dissatisfied with the healthcare service they received (1142). Care must also be taken to not rely on treatment-defined samples of younger patients but achieving a true population-based sample (145). Establishing proxy versions of the MyPOS, as proposed in the previous section, would also help in this situation. Longer and more extensive follow-up can allow subanalyses of dose-intensity and treatment type, establishing the long-term toxicity of treatment and the chronicity of symptoms and their treatment-related or disease-related nature (509,698). For this aetiologic research, potential biologic correlates of the mechanisms underlying symptom and QOL burden, particularly albumin, haemoglobin, and biomarkers of inflammatory processes (190,379,785), should be collected. However, given their rather short-term importance during acute therapies such as ASCT (379), their role for indicating longer-term poor outcomes is yet to be established.

Relating QOL information to survival and establishing the predictive power of the MyPOS for survival in myeloma could underscore the validity and equivalence of PRO information as outcomes. So far, only treatment response and disease activity are being monitored in myeloma on a regular basis, but have proven limited usefulness for indicating the need for palliative care referral. QOL needs to be established as a similarly reliable and valid indicator for progression of illness and palliative care need in the haematological cancer population. While symptom measures have been shown to be predictors of cancer survival in solid tumours (146,1143), this evidence is lacking for multiple myeloma or restricted to studies examining symptom scores recorded at baseline or at enrolment in a clinical trial (22,23,242). Predictive models that take into account more heterogeneous, larger, non-treatment defined samples are needed.

Further to these suggestions for extending the longitudinal study, new areas for observational research, particularly regarding palliative care involvement in multiple myeloma care, should also be considered. As established in the meta-analyses of place of death and specialist palliative care involvement in multiple myeloma and other haematological cancer (137,152,159,706),

haematological cancer patients are missing out on palliative care. But there is also a general lack of information on those patients that receive specialist palliative care and their preferences. We know that large proportions of patients want to die at home, but whether this proportion is comparable in haematological cancer patients and whether multiple myeloma patients maintain their preferences as the illness progresses, is not well understood (112,151,1144). Next to preferences for place of death, preferences for place of care may also change over time. Multiple myeloma, with its potentially long disease trajectory from indolent, pre-forms to advanced stages constitutes a good model for studying patient factors that help predict changes in preferences and to study advance care planning (152). This would also promote information provision and help guide resources for better quality of death and dying in myeloma (151). Linked to the study of preferences is the study of transitions in care in this patient cohort. For achieving early and good quality involvement of palliative care, the quality of existing hospice and home care programmes needs to be described. There is scope for using mortality follow-back surveys to evaluate the quality of end of life care from the caregivers' perspective (105). This would also provide insights into how myeloma patients might want to receive specialist palliative care – as part of oncological care, as a stand-alone intervention and in which setting (homecare, hospice, hospital) (161). This information could help support haematologists in their complex decision making processes when patients reach the advanced refractory stage of treatment (1145).

Disproportionally little attention has been paid to informal caregivers of multiple myeloma patients. So far, only one study measured their unmet needs and contrasted them with those of their partners with advanced multiple myeloma (90). In the haematopoietic transplant population a study has looked at long-term effects of 177 transplant survivors and their partners a median of six to seven years post-transplant (1146). Partners reported increased fatigue, cognitive problems, depressive symptoms and lower emotional, social and spiritual well-being, highlighting the adverse effects that informal caregivers suffer. It is unknown how far the evidence from caregivers of solid tumour patients with advanced disease can be extrapolated to multiple myeloma. Although multiple myeloma affects the whole family and caregivers assume responsibility in the daily care of their partners like in other cancers, the situation of myeloma sufferers and their families might be unique as caregivers might be subject to psychosocial fatigue, a process described in a recent qualitative study by Zabora et al. (2015) (360) in which stressors from years of medical caregiving, from the indolent, watch-and-wait period to the advanced stages, culminate and result in psychological and social strain.

Research is needed to describe the burden of caregiving in this population, to characterise the caregiving experience, particularly across the myeloma disease continuum. Caregiving intensity might vary, based on a number of treatment-, disease- and patient-related factors, as well as the level of disease burden in the elderly caregiver (1147). Ideally, a study should follow caregivers

over time and assess their views on their health and caregiving burden at the same time intervals during which the patient is surveyed. Given that multiple myeloma afflicts the elderly and their informal caregivers therefore also constitute an elderly population, attention should be paid to the caregivers' disease burden. Multiple myeloma often presents with a prolonged illness trajectory, characterised by patients experiencing a high level of uncertainty and fear of relapse (360,361). It would be interesting to see whether trajectories of physical, emotional, social and spiritual wellbeing match those of patients or whether transitions occur at different time interval to patient's status. A different avenue for research consists of contrasting patient's assessment with the caregiver's assessment of the patient's situation and understanding the factors that influence the agreement between the two perspectives.

Caregiver burden is partly a result of the responsibilities of caregiving, involving direct care, indirect care and the changes to normal routines and employment as a result of these responsibilities (1148). Yet, in multiple myeloma nothing is known about the actual amount of caregiving and the different tasks that informal caregivers perform when caring for their partners. This could be accomplished by incorporating self-report data about care activities, for instance through tools like the Client Receipt Service Inventory (CSRI) (1149-1151). The CSRI provides information about service utilisation by collecting retrospective information about the services received. In addition, it records the different tasks that informal caregivers perform, thus allowing the estimation of informal care costs. It is a validated tool and has been used in a range of research studies including in mental health, community care of older people and dementia (1150,1151). The study of unmet needs represents another fruitful avenue for study, with the potential to design interventions that directly address unmet needs and provide targeted care and support for informal caregivers. Two recent studies in HSCT populations have identified unmet needs in caregivers including managing concerns for cancer recurrence, finding information about financial support and benefits, strategies to maintain the caregiver's own health, sexuality and balancing the needs of the patient with the caregivers' own needs (1152,1153). These unmet needs could be further investigated in caregivers of myeloma patients. Specific assessment instruments like the Carer Support Needs Assessment Tool (1154) encompass multidimensional needs of family caregivers and have a special focus on end-of-life care, another gap present in the literature on informal caregivers in multiple myeloma. The longitudinal description of unmet needs would eventually indicate when during the disease trajectory informal caregivers are at the highest risk of experiencing strain and would benefit from support. The implementation of such tools in routine clinical care can help oncologists and palliative care providers to better identify the needs of unpaid carers and to design and offer interventions (1155,1156).

8.5.3 Using MyPOS to foster integration of haematological and palliative care in multiple myeloma

8.5.3.1 Early identification and early palliative care for patients with multiple myeloma

The new definition of palliative care by the World Health Organisation highlights the need for early identification and impeccable assessment as elements of good palliative care (266). In fact, timely referral of lung cancer and advanced solid tumour patients to palliative care has shown the potential of incorporating patient and family wishes into care plans, improving quality of life and reducing aggressive interventions in the last months of life with patients being able to die in their preferred place of care (172-174). Evidence supports the efficacy of palliative care for improving clinical outcomes and quality of care (1157), reducing hospital costs (272,1158) and reducing the aggressiveness of care in terms of hospitalisation rates, invasive procedures and intensive care admissions (1159).

All these outcomes would benefit patients with multiple myeloma and their caregivers. Yet, most patients who could potentially benefit from palliative care are not identified or are identified late in their disease process, despite higher inpatient mortality and at least comparable if not higher unmet needs (9). The significantly later access to PC services in haematology has been described in several case series and studies with aggressive lymphoma, leukemia and myeloma patients (101-104,112,126,130,137,151,243,710,1015,1160-1164). The WHO estimates that only 1 in 10 who needs palliative care receives it (111). Reasons for the low referral rates are manifold. The current system of referrals relies entirely on physicians, however, most have been slow to integrate palliative care into their practices (1165-1167). Reasons for delayed or lack of referral might include a perceived lack of palliative care needs among these patients by the haematologists, the possibility of cure in the advanced disease setting or the blurring between curative and palliative treatments in haematological cancer patients, general uncertainty in the disease trajectory, a strong sense of responsibility to provide care, stigma or lack of understanding what palliative care is and the lack of randomised controlled trials of early palliative care in haematology (103,139,141-143). Moreover, there are special considerations to care provision at the end of life in haematological cancer patients, due to the invasive nature of their treatments, the speed of change to a terminal event, the need for blood products and the fact that patients sometimes show signs of recovery even when close to death (138). Communication between providers and variation in referral criteria or in the perception of what constitutes a palliative care patient have also been proposed as chief barriers to the provision of palliative care services (1067,1168-1171).

Some of these issues, particularly regarding the speed of change and the lack of an easily recognisable advanced phase of illness, are comparable to the situation in non-malignant disease

(694). To help remedy the under-identification and late referral of haematological cancer patients, it would be possible to learn from solutions proposed in the context of non-cancer disease. A number of tools for the systematic identification of palliative care patients have been developed in recent years. These tools either focus on the systematic identification in primary care or in the emergency department or intensive care unit (179,1172-1174). They are intended to facilitate shifting the provision of palliative care from the last days of life to earlier phases, during which palliative care would be provided concomitantly with disease-modifying treatments. This enables timely modification of goals of care and the anticipation of needs (1175). Early integration shifts the delivery of palliative care from a cross-sectional to a longitudinal model, beginning at the time of a life-limiting diagnosis and continuing over the illness trajectory (1176). However, although most of these tools consider patient factors such as functional performance status or presence of comorbid illness, only a few incorporate a genuine needs-based approach to screening by recording symptom burden (1172,1173). The consensus statement on referral criteria for palliative care in the hospital setting does not consider a full symptom screening either, albeit mentioning admission due to difficult to control symptoms alongside the surprise question, frequent admissions, complex care requirements and decline in functioning as primary criteria for referral (1110). Though symptom burden is included, self-report measures are not considered in the assessment, with a clinician usually making an informal assessment of overall symptom burden. But the presence of symptoms is regarded as a trigger equal to factors such as healthcare resource use and living situation (1173). This is questionable as it has been shown that single criteria alone, such as the surprise question or performance status, are not specific enough and may identify too many patients, and they do not reflect and capture the complexity of need (106,694,1177,1178).

For effective identification of myeloma patients in need for palliative care, a shift in prognostication from prognosis/survival models to needs-based models, identifying those at risk of deterioration for proactive assessment and care planning, is needed (1173). Screening criteria should rely on self-reported, systematically assessed symptom burden. Assessment should be multidimensional in nature, incorporating those aspects important to patients and their caregivers (1179). These features are offered by the MyPOS. What is lacking is a set of criteria for its items that could be used to screen for appropriate referral to SPC in multiple myeloma patients. This study would need to establish the diagnostic validity of these cut-off criteria in a large haematological/multiple myeloma population. Additionally, for those referred to SPC according to these criteria, the appropriateness of each referral to SPC should be determined. Three sets of cut-off criteria on the MyPOS should be developed to determine the level of SPC that is needed, (a) a one-off consultation with SPC due to low palliative care needs, (b) medium amount of contact with the SPC team due to a moderate number of palliative care needs, and (c) a high amount of contact with the SPC team due to a high and complex palliative care needs.

Similar routine screening procedures have already been developed for distress screening in general oncological practice. Since the National Comprehensive Cancer Network in the USA (647) and the National Institute for Clinical Excellence in the UK (1180) designated the Distress Thermometer as the main instruments in their guidelines, it is now the most widely implemented clinical tool for screening in psychosocial oncology. A similar process could be designed for incorporating the MyPOS into standard oncological practice. Also, new technology in form of touch-screen computers installed in outpatient clinics could help this process, as already piloted in several UK clinics in the Imparts project (1181). The set of diagnostic criteria could be obtained in a prospective study among multiple myeloma patients in outpatient clinics. However, since the main aim would be to obtain valid and reliable criteria, a sample of consecutive patients needs to be screened for the criteria to be generalizable. This poses interesting demands on the recruitment process. Ideally, the MyPOS should be implemented as a routine screening tool for all patients in clinics and recruitment should follow an opt-out approach. Several demographic and clinical characteristics could be taken into account when designing the set of criteria for the MyPOS. These screening criteria could either consist of a cut-off value for subscales of the MyPOS or could consider particularly high values on a set of items (i.e. levels "3 – severe" and "4 – overwhelmingly" on the MyPOS scale). For instance, instead of defining a value on one subscale, one could design a criterion of at least two scores of "4" or at least three scores of "3" on the whole MyPOS or among the physical or the psychological items.

To determine the optimal cut-off points on the MyPOS for appropriate referrals to the palliative care consultation service, an external, standard criterion needs to be defined. This could either consist of a palliative care clinician's rating of appropriateness of SPC for each patient, or – in a longitudinal study – survival. However, this again poses problems, as both these criteria represent those barriers that were identified as needing to be overcome for timely referral of haematological cancer patients to palliative care. In the absence of a clear definition of what constitutes a palliative care patient (1068), this situation cannot easily be remedied. All potential external criteria, even the ESAS for which cut-off criteria have been defined (1182,1183) and the surprise question to determine prognosis (1184), carry a potentially substantial amount of measurement bias and cannot therefore be considered gold standards. This poses challenges for the evaluation of the diagnostic validity of these cut-off criteria since ROC curve analysis and generalised linear models procedures for determining the set of criteria with the smallest amount of misclassification rely on a criterion that is unbiased by measurement error. Also, determining the appropriate cut-off score to use on the MyPOS depends on the clinical importance of false positives versus false negatives. One could argue that it is more important that every patient with multiple myeloma who possibly has a need for palliative care interventions be identified (531) – which would argue for favouring sensitivity over specificity. This approach might result in a potentially large

population of multiple myeloma needing attention from SPC services, thus putting the service under considerable strain. Therefore, an economic evaluation should be performed alongside this validation study.

A possible alternative solution would be to develop training for haematology doctors and nurses to deliver general palliative care. This longitudinal study has demonstrated that advanced disease and palliative care need are not dependent on phase of illness or biological factors. Rather, symptom burden, even during the early phases of illness indicate that patients can profit from symptom alleviation and psychosocial interventions. Information needs, also regarding the end of life, are high in this cohort and need to be addressed (1185). A shared care model is proposed for facilitating the integration of palliative care and haematological care, whereby general palliative care consists of alleviation of pain and other symptoms, psychosocial care of anxiety and depression and general discussions regarding prognosis, care plans and end of life care. Specialist palliative care services could be involved on a short-term basis for the care of complex and refractory symptoms and side effects in myeloma. The following model (Figure 13), partly based on Hui and co-authors' (2015) views on early integration of palliative care in general oncological care (260) highlights some of the SPC contributions to generalist palliative care in haematology. The upper row represents generalist palliative care issues, the lower row represents contributions of SPC to the care of myeloma patients.

Figure 13: Research opportunities of generalist and specialist palliative care in multiple myeloma (based on (260))

	Early or advanced multiple myeloma	**Advanced and refractory myeloma**
Disease and cancer treatment-related issues	Secondary supportive care to cancer treatment (addressing toxicities in MM treatment) Management of treatment-related side effects	Cancer treatment decisions at the end of life
Supportive care issues	Physical, emotional, spiritual concerns Unmet needs, particularly information needs and sexual concerns Advance care planning	End of life care issues in patients with cancer Palliative home care

An intervention to support such an approach would be the routine use of the MyPOS for monitoring of symptoms and palliative care concerns in myeloma patients. Some recent studies in general oncology and HSCT populations using website-based systems have shown how this application can be successfully linked to patient education and offering personalised supportive care through these websites (43,189,467,569,1186-1188). The self-care element combined with

patient education has the potential to foster self-efficacy and empower patients (421,1189-1191). Trials have shown the feasibility of building a monitoring system using the internet even in older populations (43). Monitoring applications can either be built as patient-led systems, in which patients monitor their QOL themselves, or as clinician-led systems, in which monitoring is linked to an alert system notifying the clinic of the need to review the patient, thus providing early identification and further treatment of symptoms and problems. In the last part of this section, I would like to propose this latter approach for a complex intervention study. However, designing an intervention that puts monitoring into the hands of the patients, together with appropriate support for self-help and further interventions also represents a fruitful way of enhancing the clinical utility of PROs such as the MyPOS.

8.5.3.2 Complex intervention of monitoring HRQOL and palliative care needs in multiple myeloma using the MyPOS

Instead of just introducing the measure into practice I would like to propose combining MyPOS monitoring with a training component for oncology staff (1160) and a restructuring of the multidisciplinary team meeting process in haematology, thereby addressing some of the shortcomings that have been identified to hamper the evaluation of routine outcome assessment in clinical practice. According to Greenhalgh (2005) (427), PROs can be applied at the individual patient or the group level. At the individual level, screening and monitoring with feedback only provided to the health care professional (HCP) directly involved in the care of the patient is the most widely studied model. No intervention study to date has addressed the gap of implementing outcome measures as tools to structure the process of care planning in multi-disciplinary team meetings (MDTs) (426). This study would also need to address shortcomings in trials of outcome measures, namely implementation approaches that foster sustainable, local ownership, training in the use of PROs and continued training for health care professionals, provision of management guidelines, and thus providing a whole-systems approach to implementation (472).

Two reasons in particular have led researchers and clinicians to campaign for the wide-spread and routine use of PROs in clinical care. First, disconcordance between patient-reported and clinician-reported symptoms and the unreliability of symptom assessment has been observed. Basch et al. (2006, 2009) (44,412) report that cancer patients detected symptoms sooner and with a higher severity than oncologists and that clinicians who independently graded adverse events within minutes of each other reached modest levels of agreement at best (413). Systematic underreporting of symptoms by clinicians, in terms of frequency, severity, incompleteness, and general heterogeneity in the methods of reporting have also been observed in other studies in oncology (414,1192). Second, next to the improvement of accuracy in the assessment of

symptoms, PROs are hypothesised to help the issue of clinician's reluctance to address QOL issues in consultations (427), an issue that was highlighted by clinicians participating in the focus group for development of the MyPOS (384). In particular, they valued the MyPOS as an "icebreaker" to discuss difficult or embarrassing questions such as emotional and sexual functioning with patients. Systematic introduction of PROs into clinical care may enable clinicians to discuss these issues and bring about a change in attitudes, so that they view QOL as clinically important enough to initiate changes in treatment (427).

Despite recommendations, the routine use of PROs in palliative care has been slow to implement and their wide-spread use is yet to be achieved (37,472). The majority of available evidence, both from cancer and in palliative care, focuses on the one-off application. Twelve systematic reviews exist (37,416-424,26,453,966). They conclude tentative evidence regarding the effectiveness of PROs to improve quality of care, with contradicting results depending on the patient population and outcomes that are studied. Particularly in palliative care (37), the introduction of PROs has not yielded the impact on patient outcomes that investigators had hoped for. While there is a strong effect for their impact on processes of care, both in form of better recognition of symptoms, better communication regarding QOL issues and more actions taken as a result (37,416,418,427,1193), the evidence for their influence on outcomes shows minimal to moderate effects (37). The lack of impact of PROs has been attributed to both their method of use as well as to implementation factors of the intervention (427). Without further elements of the intervention (e.g. training and clinical management guidelines) addressing changes in staff attitudes and behaviour, it is unlikely that the simple introduction of a screening measure leads to changes in clinician attitudes and behaviour and ultimately to changes in patient care (427). Reviews of facilitators and barriers during the implementation of outcome measures into routine care also point towards the importance of a thorough model of implementation that takes into account the organisational background and interpersonal relationships between team members for the intervention as a backdrop to be successful (416,472,1194,1195).

Providing PROs for screening purposes with results discussed by doctors alone misses the reality of clinical care and the opportunity to make use of the multidisciplinary team meetings that are also slowly implemented in haematological care. MDTs in cancer care are composed differently than MDTs in palliative care. Their focus often is on diagnosis and curative treatment decisions rather than consisting of an inter-disciplinary, multi-professional team to discuss symptom alleviation and adaptation to advanced illness, as is the case for palliative care (434). However, with the introduction of outcome measures such as the MyPOS and incorporation of this information to plan care, it could be possible to alert clinicians to the wider, multidimensional spectrum of unmet needs in the multiple myeloma population and help teams to plan care and to refer patients appropriately to supportive, psychosocial or palliative care services if needed.

MDTs are the preferred model of service delivery in palliative care and neurorehabilitation (434) and have been shown to enhance decision making, coordination of care and clinical outcomes (1063). Only a small number of qualitative or non-randomised studies has studied introduction of PROs in MDTs, using information from PROs as a determinant of clinical decisions (1196-1198). These studies solely originated from the discipline of rehabilitative medicine. Only one study within palliative care could be located (437).

Routine use of PROs such as the MyPOS in haematological MDTs could yield many potential benefits for myeloma patients, i.e. improved symptom identification, patient-centred care plans, better communication within teams and between care providers, the patient and their caregivers, as well as enhancing quality of care (1199). If PROs are thoroughly implemented in MDT meetings with appropriate training provided to all clinicians, this intervention could potentially help with designing better care plans for patients reflecting the multi-dimensional nature of unmet needs, and making the process of clinical decision making a shared process (427).

Evaluating this intervention would need to follow the Medical Research Council's framework for complex interventions (1200). As the introduction of PROs change clinician behaviour and processes of care, the introduction of the MyPOS is a complex intervention. It affects other care processes (427) and a number of intermediate outcomes need to be achieved before more distal outcomes like patient health status can be affected. Establishing its effectiveness can only succeed if the active ingredients have been identified (1201). This entails determining elements that lead to successful implementation, both in form of incorporation of PROs / change in existing processes of care and in form of training. Careful qualitative modelling of team processes in MDTs is necessary to understand the mechanisms underlying successful change (434,1202), before such an intervention can be evaluated. Therefore, qualitative phases should precede a feasibility study/phase II trial to test the feasibility of evaluating the introduction of the MyPOS into routine clinical care. Only then can a full phase III efficacy RCT be successful. Moreover, since the intervention targets care processes with the risk of carry-over and contamination bias, an RCT would need to employ a cluster design (1203) with implications for costs through sample size and increase in number of recruiting centres not feasible until best methods of implementation have been determined.

The feasibility study should also explore the best outcomes to evaluate such an intervention. Greenhalgh (2005) (427) has pointed out that often outcomes too distal are chosen, without an understanding of the intermediate processes that need to occur for distal outcomes to be affected. Santana et al. (2014) (1199) have proposed a cascade of processes and outcomes that can be affected by the introduction of PROs in clinical practice. They define communication and patient engagement/activation as processes most proximal to the intervention, followed by shared

decision making, changed patient management, patient and clinician satisfaction, to most distal outcomes such as patient adherence and outcomes in the form of health care use, health status/HRQOL and survival. Reviews of the effectiveness of PROs in clinical practice (37,416-424,426,453,966) also highlighted that choice of outcome measures to evaluate the intervention are not guided by a theoretical model of what is affected in what way by the intervention. For the introduction of the MyPOS in MDTs in haematology, this aspect needs to be modelled both in the qualitative phase I work and the phase II feasibility study. Some qualitative work exploring team processes after introduction of PROs has been undertaken in neurorehabilitation (434), identifying meeting structure organisation and model of service delivery as the external constraints, and leadership and team/social climate as mediating processes. Another study exploring how these teams use measurement tools highlighted that although the tools led to a better identification of patient's problems and also were used externally, to justify and demonstrate the effectiveness of their care to managers and external agencies like social care services, the interpretation of the scores to guide clinical decisions was hampered by the clinician's lacking familiarity with the tools and divergent professionals perspectives on what constitutes an important score (37,43,436,1204,1205). The intervention therefore needs to address this need for training. Development, planning of the training, the choice of the training approach, the content of the training and delivery as well as supporting materials and duration of training sessions, lastly the sustainability of training effects with staff turn-over should be decided upon. I propose for the training intervention to combine problem-based interactive learning elements with small group interactive learning practice and the possible introduction of dedicated "outcome champions" within each organisation to support the introduction of PROs in team meetings. The training element would thus combine elements of train the trainer, focus on team processes, communication and problem solving strategies, incorporate clinical management guidelines for frequent HRQOL problems in multiple myeloma and refresher webinars for maintenance of skills. Both the phase II and phase III stages of evaluation should incorporate qualitative components, particularly non-participant observation of team meetings, to understand the above described team processes and whether the intervention is having an effect on these processes.

However, despite this intervention addressing several of the shortcomings identified by Greenhalgh in the evaluation studies of PROs (427), it will prove challenging to obtain a large enough number of centres to participate in this multi-centre study. While the feasibility study can follow a quasi-experimental design, possibly using a pre-post study with a patient cohort being followed before the introduction of outcome measures and a second cohort of consecutive patients after the introduction of the MyPOS, the phase III study will need to employ a cluster randomised design with enough centres participating to account for the intracluster correlation of observations and the lower power associated with such a design (1203). However, since haematology

constitutes a discipline relatively naïve regarding routine use of patient-reported outcome measures this trial could be successful. The aspect of long-term sustainability of these changed processes of care requires the use of implementation methods (1206).

8.6 Conclusion

This observational study to describe the longitudinal trajectories of QOL in multiple myeloma provides a major contribution towards the understanding of the persistent and severe QOL and palliative care-related problems and concerns in this patient group. It illustrates the high burden of symptom prevalence and psychological distress experienced by those patients in all stages of myeloma disease, from newly diagnosed into the advanced, refractory disease stages. People with multiple myeloma rarely receive adequate support for the wider symptom, psychological and other multidimensional problems and they are not accessing specialist palliative care services. This study was the first to identify and describe four QOL trajectories within the heterogeneous group of myeloma patients. While there are two groups experiencing good and stable or improving QOL, there are also subgroups with a chronically low level of QOL or deteriorating QOL.

Experiencing a trajectory of poor QOL was not related to the disease phase or staging variables of the disease, like the International Staging System. This points towards the need to base advanced support for these patients not on a model of prognosis but on one of palliative care need. Predictors for experiencing a trajectory of poor or deteriorating QOL were general symptom level, pain or fatigue and psychological distress (anxiety and depression). In order to identify these patients early and to adequately refer them to palliative and supportive services, symptom burden and psychological distress therefore present as targets for routine assessment. In an extensive psychometric analysis of the Myeloma Patient Outcome Scale, a newly developed myeloma-specific QOL tool to measure these aspects of symptom burden and psychological distress, items were evaluated for their longitudinal measurement properties to support such individual patient-monitoring. By changing the model of care for myeloma patients, via the early integration of palliative and supportive care services with routine screening procedures using PROs in the wider myeloma population, barriers to palliative care access in this haematological patient group could be addressed. Further research is needed to test the generalisability and clinical applicability of this prognostic model in routine clinical care.

As well as identifying the targets for routine patient-monitoring, this study also presented methodological contributions to longitudinal research and psychometric analysis. These include methods of longitudinal follow-up and the successful application of a new type of longitudinal analysis that combines cluster analysis with mixed effects modelling, the latent growth curve

analytical approach. This approach allows the identification of subgroups of homogeneous trajectories within a sample characterised by heterogeneity. This heterogeneity would otherwise be obscured when using analytical approaches that focus on the average trajectory for a group of patients. The second methodological contribution consists in defining and evaluating more stringent psychometric criteria for the application of monitoring individuals, an approach that has not yet been developed in classical and new psychometric test theory. The Rasch measurement model alongside with new approaches to determine the responsiveness of change and to assess different forms of longitudinal reliability were applied to the psychometric analysis of the MyPOS.

Overall, this study has shown that longitudinal description of QOL trajectories can identify important targets for monitoring and intervention in the group of patients with multiple myeloma. There is scope to generalise these findings to other more chronic, yet incurable haematological conditions increasingly afflicting elderly patients. Whether the proposed model of predictors can be validly monitored needs to be tested in an intervention study.

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10 Appendix A: Correspondence with the Research Ethics Committee: approvals and amendments

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09 October 2013

Professor Irene Higginson
Professor and Head of Department
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Dear Professor Higginson

Study Title: **Quality of life in multiple myeloma (MyCare): Longitudinal experience and potential use of information on quality of life for patient self-monitoring and patient care**

REC reference: **13/LO/1140**
IRAS project ID: **129254**

The Research Ethics Committee reviewed the above application at the meeting held on 25 September 2013.

Documents reviewed

The documents reviewed at the meeting were:

Document	*Version*	*Date*
Advertisement	Recruitment Poster v:1	16 July 2013
Advertisement	Recruitment Leaflet v:1	16 July 2013
Covering Letter		16 July 2013
Evidence of insurance or indemnity	KCL	01 August 2013
GP/Consultant Information Sheets	Patients Phases 1-III v:1	16 July 2013
GP/Consultant Information Sheets	Carers phase II v:1	16 July 2013
Investigator CV	Professor Irene Higginson	12 July 2013

Letter from Statistician	Letter from Dr Wei Gao, KCL	04 June 2013
Other: Myeloma UK grant award letter		08 January 2010
Other: Letter from funder St Christopher's Hospice		20 May 2011
Participant Consent Form: Phase 1 - Pilot QoL Survey	1	16 July 2013
Participant Consent Form: Phase II - Longitudinal Survey Patient	1	16 July 2013
Participant Consent Form: Phase II - Longitudinal Survey Carer	1	16 July 2013
Participant Consent Form: Phase III - Patient focus group	1	16 July 2013
Participant Consent Form: Phase III - Clinician focus group	1	16 July 2013
Participant Information Sheet: Phase 1 - Pilot QoL Survey	1	16 July 2013
Participant Information Sheet: Phase II - Longitudinal QoL Survey Patient	1	16 July 2013
Participant Information Sheet: Phase II Longitudinal QoL Survey Carer	1	16 July 2013
Participant Information Sheet: Phase III - Patient focus group	1	16 July 2013
Participant Information Sheet: Phase III - Clinician focus group	1	16 July 2013
Protocol	2	04 July 2013
Questionnaire: Client Services Receipt Inventory CSRI		
Questionnaire: Global Mastery Subscale (Pearlin, 1981)		
Questionnaire: EORTC QLQ C30		
Questionnaire: EORTC QLQ MY20		
Questionnaire: Hospital Anxiety and Depression Scale (HADS)		
Questionnaire: Patient EQ-5D-3L		
Questionnaire: Zarit Burden Interview Short Form 12		
Questionnaire: Patient Outcome Scale Carer	2	
Questionnaire: Carer EQ-5D-3L		
Questionnaire: Myeloma-specific quality of life MYPOS	3	
Questionnaire: Data collection form for patients	1	16 July 2013
Questionnaire: Data collection form for carers	1	16 July 2013
Questionnaire: Data collection form for clinicians (phase III focus group)	1	16 July 2013
Questionnaire: Data collection for non-participants	1	16 July 2013
REC application		16 July 2013
Referees or other scientific critique report	Synopsis of peer review comments - response from applicants	26 November 2009

Provisional opinion

The Committee reviewed the above application.

In discussion the Committee noted the following issues:

- The Lead Reviewer introduced the study. This is a student project for a PhD qualification. The study aims to assess how the quality of life changes over time for people who have Myeloma. In addition, the study will examine whether existing questionnaires about quality of life can be used by people with Myeloma themselves to measure their own quality of life changes.

The Second Reviewer was unable to attend the REC meeting, but submitted written comments as follows:

Longitudinal Quality of Life in Multiple Myeloma

- I have read the application thoroughly and note that it is a fairly dense research student application which is also attached to some large grants (£250,000 and £148,970.) The study aims to look at the quality of life for people with myeloma in order to focus their care accordingly. It uses questionnaires over periods of time and does not involve their medical treatment.

Comments/concerns

- I note the word 'treatment', it is frequently used in the Information Sheet but think it should be more carefully considered as the aim of this study is to see how to improve the wellbeing and the care of the patients, not improve their treatment. I think it is important to be clear about this.

- It may be worth asking whether there is some validity in the Peer Review opinion that the research may be too complex for a meaningful result and that current tools are just as good.

- There are 5 sources of information (3 Surveys and 2 Focus Groups). In the first, just 5 people will take part in the Pilot Survey researching whether certain groups of people have a better or worse quality of life and I wonder if this enough?

- In the two 'Change in Quality of Life Over Time' Surveys, one addresses the Patients and one addresses the Carers. Whilst there may be an assessment of the quality of life of the Carers there is no suggestion that their needs will be addressed which could impact on the quality of life of the people they care for and clarification is sought as to whether this has taken into account.

- Secondly, it is assumed that the carer will be caring for a 'relative' which is too restrictive and unlikely to always be the case.

- There are two Focus Groups aimed at patients and clinicians. The application at p.21 mentions the availability of a 'distress protocol' to be followed in the event of any upset caused. This is not mentioned in the Information Sheet other than that they may be able

to withdraw from the study or not answer the question. A more fulsome description of support should be available in the Information Sheet.

- Generally it is difficult to know whether this research is instructive with respect to the validity of the information and the applicability to a working model of Quality of Life in Myeloma.
- In addition, the Committee noted the majority of participants will be asked complete two sets of Questionnaires which they feel are fairly extensive and may cause considerable burden to participants.
- The Committee noted the pilot study only has five participants and wonders if the sample is adequate.
- The Committee noted that patients will monitor their own changes, but also notes that this is not covered in the Information Sheet.
- The Committee noted that large parts of the application was copied from the protocol and pasted into the application, most of which was not relevant and unhelpful to the Committee.
- The Committee seeks clarity as to whether access to medical records is required as it is not clear from the application.
- The Committee notes that participants who become distressed will be excluded from the study and wonders if this will distort the research as many participants will be upset and capturing some of the feelings around this could be useful to the research.
- The Committee notes this is a longitudinal study and wonders if eight months is long enough to get results on an individual's quality of life study.

The Chief Investigator, Prof Irene Higginson did not attend the review of the study, but was represented by, Ms Christina Ramsenthaler, Student on the project.

The Chair introduced the Observer and advised the Researcher of the procedure regarding the Observer's responsibility to maintain the confidentiality of the meeting. The Chair also advised the Researcher that the Observer would leave the meeting if he wished.

- The Researcher gave an overview of the study. She confirmed that access to participant's medical records will be given to the research team at King's College London, Guy's and St Thomas and St Christopher's, but mainly herself as the student and two Research Nurses.
- The Researcher confirmed that screening for the study will be carried out by the medical team in the centre who will advise her who has satisfied the inclusion criteria.
- The Researcher was asked how distress in a participant will be judged. The Researcher told the Committee that it is easy to identify if a participant is distressed from their persona and their discussions with the Nurse. The Researcher assured the

Committee however, that patients awaiting chemotherapy will not be approached.

- The Researcher was asked about excluding distressed patients from the study in relation to the results of the study. The Researcher informed the Committee that this exact point had been discussed thoroughly, but decided to take this approach as exclusion of these patients had been done in previous studies. The Researcher told the Committee that there are no standard guidelines to judge a patient's level of distress, but that clinical judgement was the best way to tackle this. The Researcher went on to say that the clinicians know their patients very well and their judgement can be trusted.

- The Researcher confirmed the consent procedure with the Committee. She stated that potential participants are identified by the clinical team. Participants are then given a leaflet about the study and if they are interested in the study, they will be approached by a member of the research team who will then give them an Information Sheet about the study. Thereafter the participant will be approached and any questions they may have are answered at this time. The participant will then be given a further 24 hours to make a decision to join.

- The Committee discussed the self-monitoring aspect of the study with the Researcher. The Researcher confirmed that details of this will be discussed in the focus group.

- The Researcher discussed the pilot study with the Committee. The Researcher informed the Committee that the purpose of the pilot study was to test the Questionnaires before rolling out in to the main study. She said that five to seven participants are sufficient for this.

- The Researcher confirmed that participants can complete the Questionnaires at home if they prefer, or they can complete them in the clinic. She also said that the Questionnaires will take about 30 minutes to complete and that if patients want to complete the Questionnaire in the clinic they will be taken to a comfortable area within the Institute.

- The Committee asked about the exclusion of patients who are neutropenia. The Researcher informed the Committee that if the patient is on the follow up study, person to person contact is not necessary as questionnaires can be posted.

- The Committee asked about the length of the study, as to whether it is long enough to get longitudinal data. The Researcher informed the Committee that survival rates are approximately 18 months so it is believed that this is enough time. The Researcher also said that the study duration was also determined by funding restrictions.

The Committee would be content to give a favourable ethical opinion of the research, subject to receiving a complete response to the request for further information set out below.

Authority to consider your response and to confirm the Committee's final opinion has been delegated to the Chair.

Further information or clarification required

The Committee discussed the Researcher's responses further and felt that a number of

issues required further confirmation, information and/or clarification as follows:

i. The Committee commented that although they are satisfied with the consenting process, the Researcher is to ensure that patients who are willing to complete the Questionnaire at the clinic are taken to an appropriate area to do so and should not be done in the clinic.

ii. The Committee asks the Researcher to add information about the distress protocol to the Information Sheet explaining what it is and how it will be used if required. Similarly, the Researcher is asked to add information about the distress protocol for the focus group.

iii. The Committee asks the Researcher to confirm whether five or seven participants are required for the pilot study.

The following amendments should be made to the Patient Information Sheet:

iv. The Committee notes that the word treatment is frequently used but thinks it should be more carefully considered as the aim of this study is to see how to improve the wellbeing and the care of the patients, not improve their treatment. The Researcher is therefore asked to change the word to assessment.

v. The Committee asks the Researcher to spell out in the Information Sheet that participants will be expected to monitor their own changes.

vi. The Committee asks the Researcher to clearly spell out the frequency of the Questionnaires and to ensure that both the patients and their carers are aware of the level of commitment that is required for the study.

vii. The Committee asks the Researcher to amend the section in the Information Sheet that says "some find it convenient to complete the Questionnaire"; the Committee believes the word "convenient" is inappropriate.

viii. The Committee asks the Researcher to add a paragraph that explains why access to medical records is required, who will have access to the records and what the records will be used for. This should be reflected in the Consent Form.

The following amendments should be made to the Consent Form Sheet:

ix. The Committee asks the Researcher to ensure that amendments made to the Information Sheets are reflected in the Consent Form where appropriate.

Decision: Provisional Opinion

The Committee concluded that a provisional favourable opinion be given to the study, subject to receipt of further information/clarification set out above. The Committee delegated authority to the Chair in consultation with two other Members for considering the further information and confirming the REC's final opinion if satisfied with the response obtained.

The REC nominated the Co-ordinator to be the point of contact should further clarification be sought from the application upon receipt of the decision letter.

If you would find it helpful to discuss any of the matters raised above or seek further clarification from a member of the Committee, you are welcome to contact Audrey Adams on 020 7972 2584.

When submitting your response to the Committee, please send revised documentation where appropriate underlining or otherwise highlighting the changes you have made and giving revised version numbers and dates.

If the committee has asked for clarification or changes to any answers given in the application form, please do not submit a revised copy of the application form; these can be addressed in a covering letter to the REC.

The Committee will confirm the final ethical opinion within a maximum of 60 days from the date of initial receipt of the application, excluding the time taken by you to respond fully to the above points. A response should be submitted by no later than 08 November 2013.

Membership of the Committee

The members of the Committee who were present at the meeting are listed on the attached sheet.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

13/LO/1140	**Please quote this number on all correspondence**

Yours sincerely

Pp Dr Andrew Hilson
Chair

Email: NRESCommitte.London-Central@nhs.net

Enclosures: *List of names and professions of members who were present at the meeting and those who submitted written comments.*

Copy to: *Mr Keith Brennan, King's College London*

NRES Committee London - Central

Attendance at Committee meeting on 25 September 2013

Committee Members:

Name	*Profession*	*Present*	*Notes*
Sir Adrian Baillie	Financial Investment Advisor	Yes	
Mr Clive Carsley	Retired Lawyer	Yes	
Sally Davis	Lawyer/PhD Student	No	
Dr Olivia Festy	Clinical Trials Administrator	No	
Mrs Sophie Forsyth	Lawyer	Yes	
Dr Frances Goodhart	Consultant Clinical Psychologist	Yes	
Dr Andrew Hilson	Consultant in Nuclear Medicine	Yes	
Dr Leslie Huson	Consultant Medical Statistician	Yes	
Mr Roy Sinclair	Pharmacist	Yes	
Professor Lewis Spitz	Emeritus Nuffield Professor of Paediatric Surgery	Yes	
Mr Benjamin Stanfield-Davies	University Lecturer	Yes	
Dr Gareth Tudor-Williams	Consultant in Paediatric Infectious Diseases	No	
Miss Zalika Xavier	Market Researcher	No	

Also in attendance:

Name	*Position (or reason for attending)*
Mrs Audrey Adams	NRES REC Manger
Ms Hayley Fraser	REC Assistant
Ms Lynda Mc Cormack	Peripatetic Co-ordinator
Ervin Shpuza	Trainee Research Nurse

School of Medicine
at Guy's, King's College and St Thomas' Hospitals

Department of Palliative Care, Policy & Rehabilitation

Professor Irene Higginson
BMedSci BMBS FFPHM PhD FRCP
Head of Department
Professor Lynne Turner-Stokes
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KING'S College LONDON

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Cicely Saunders Institute
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Dr Andrew Hilson
Chair, NRES Committee London - Central
Skipton House
80 London Road
London SE1 6LH

7th November 2013

Dear Dr Hilson,

Re: Quality of life in multiple myeloma (MyCare): Longitudinal experience and potential use of information on quality of life for patient self-monitoring and patient care
REC Ref No: 13/LO/1140
IRAS Project ID: 129254

Thank you for your letter dated 9th October, and for your helpful suggestions. We have addressed each issue below:

i. *The Committee commented that although they are satisfied with the consenting process, the Researcher is to ensure that patients who are willing to complete the Questionnaire at the clinic are taken to an appropriate area to do so and should not be done in the clinic.*

We will make sure to take those participants that are willing to complete the questionnaire at the clinic to the Cicely Saunders Institute which is located directly opposite King's College Hospital. On the ground floor of the building there are dedicated private therapy rooms available in the Macmillan Cancer Support centre which will be available for the participants to complete the questionnaire in privacy. At the other participating sites (i.e. Guy's and St Thomas' NHS Foundation Trust) appropriate areas might not be available and researchers will give participants recruited at those sites the questionnaires to complete at home only. This will be reflected in the standard operating procedures for these sites.

ii. The Committee asks the Researcher to add information about the distress protocol to the Information Sheet explaining what it is and how it will be used if required. Similarly, the Researcher is asked to add information about the distress protocol for the focus group.

We have added this information to the Patient Information Sheets for all three phases (see section 'What are the disadvantages or risks of taking part?'). We have added information on the distress protocol for the focus groups, but only for the focus group held with patients. A distress protocol for the focus group with health care professionals is not in place.

iii. The Committee asks the Researcher to confirm whether five or seven participants are required for the pilot study.

We will maximally sample seven participants for the pilot study. This number will be sufficient to capture views about the feasibility of the design and approaches used in the study from a variety of patients with different characteristics.

iv. The following amendments should be made to the Patient Information Sheet: The Committee notes that the word treatment is frequently used but thinks it should be more carefully considered as the aim of this study is to see how to improve the wellbeing and the care of the patients, not improve their treatment. The Researcher is therefore asked to change the word to assessment.

We have changed the word treatment to the word assessment in all Participant Information sheets. This was done for the sections 'What is the purpose of the study?' and the section 'What are the potential benefits of taking part?'. The word treatment in the section 'What will happen if I decide not to take part?' was changed to care as it was felt to be a more appropriate substitute for treatment in this context than the word 'assessment'.

v. The Committee asks the Researcher to spell out in the Information Sheet that participants will be expected to monitor their own changes.

We have changed the relevant section in the Information Sheet for the focus group with patients. It is only then that we will ask participants their opinions on monitoring their own changes in quality of life. During the longitudinal study with patients and carers (phase II), changes in quality of life will be assessed by the answers given in the questionnaires.

vi. The Committee asks the Researcher to spell out the frequency of the Questionnaires and to ensure that both the patients and their carers are aware of the level of commitment that is required for the study.

We have amended the Study Information Sheet for phase II, longitudinal survey, for both patients and carers. Please see the changes made to both sheets in section 'What will happen to me if I decide to take part?'. We have spelled out how often participants will receive questionnaires in total and we have described further what the questionnaires will contain. Amendments on this subject were also made in the consent forms for phase II patient survey and phase II carer survey. The total number of questionnaires patients or carers will receive is now stated in the consent forms.

vii. The committee asks the Researcher to amend the section in the Information Sheet that says "some find it convenient to complete the Questionnaire", the Committee believes the word "convenient" is inappropriate.

The section in the Information Sheet for phase I, Pilot QOL survey, was amended. The passage of text has been substituted with "at a place and time of your choice (for example your home or a private room in our research institute)".

viii. The Committee asks the Researcher to add a paragraph that explains why access to medical records is required, who will have access to the records and what the records will be used for. This should be reflected in the Consent Form.

This paragraph was added to the Information Sheets for phase I, Pilot QOL survey, phase II (both patient and carer survey), and phase II (patient focus group). In the section 'What will happen to me if I decide to take part' it describes that access to the medical records is needed to understand possible treatment factors that could have an influence on quality of life, that records will be viewed by the researchers or research nurses working on the project, and which information will be viewed. The section in the relevant consent forms for all three phases has been amended.

ix. The following amendments should be made to the Consent Form Sheet: The Committee asks the Researcher to ensure that amendments made to the Information Sheets are reflected in the Consent Form where appropriate.

The amendments made to the Information Sheets with regard to access to medical records and the frequency of questionnaires in the longitudinal patient and carer survey (phase II) are now reflected in the Consent Form.

10 Appendix A: Correspondence with the Research Ethics Committee: approvals and amendments

All changes to the Information Sheets and Consent Forms have been highlighted in red colour. We enclose the supporting documents which have been amended since the meeting of 25th September, and thank you for reviewing the amended versions. The table below lists all the documents enclosed with new dates and version numbers.

Document	Version	Date
Participant Information Sheet: Phase I-Pilot QOL Survey	2	07/11/2013
Participant Information Sheet: Phase II-Longitudinal QOL Survey Carer Version	2	07/11/2013
Participant Information Sheet: Phase II – Longitudinal QOL Survey Patient version	2	07/11/2013
Participant Information Sheet: Phase III – Clinician Focus group	2	07/11/2013
Participant Information Sheet: Phase III – Patient Focus Group	2	07/11/2013
Participant Consent Sheet: Phase 1-Pilot QOL Survey	2	07/11/2013
Participant Consent Sheet: Phase II-Longitudinal QOL Survey Carer Version	2	07/11/2013
Participant Consent Sheet: Phase II – Longitudinal QOL Survey Patient version	2	07/11/2013
Participant Consent Sheet: Phase III – Clinician focus group	2	07/11/2013
Participant Consent Sheet: Phase III – Patient focus Group	2	07/11/2013

Many thanks once again for your helpful comments and suggestions. I hope you find these amendments adequate, and look forward to hearing from you.

Yours Sincerely,

Professor Irene Higginson
Head of Department and Professor of Palliative Care and Policy.

NHS
Health Research Authority
National Research Ethics Service
NRES Committee London– Central
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Barlow House
4 Minshull Street
Manchester
M1 3DZ

Telephone: 0161 625 7434

15 May 2014 - Reissued

Professor Irene Higginson
Professor and Head of Department
King's College London
Dept Pall Care, Policy and Rehab
Cicely Saunders Institut
Bessemer Road Denmark Hill London
SE5 9PJ

Dear Professor Higginson

Study title:	**Quality of life in multiple myeloma (MyCare): Longitudinal experience and potential use of information on quality of life for patient self-monitoring and patient care**
REC reference:	**13/LO/1140**
IRAS project ID:	**129254**

Thank you for your letter of 07 November 2013, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details, unless you expressly withhold permission to do so. Publication will be no earlier than three months from the date of this favourable opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to withhold permission to publish, please contact the REC Manager Shehnaz Ishaq, nrescommittee.london-centarl@nhs.net.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database within 6 weeks of recruitment of the first participant (for medical device studies, within the timeline determined by the current registration and publication trees).

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to contest the need for registration they should contact Catherine Blewett (catherineblewett@nhs.net), the HRA does not, however, expect exceptions to be made. Guidance on where to register is provided within IRAS.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Advertisement	Recruitment Poster v:1	16 July 2013
Advertisement	Recruitment Leaflet v:1	16 July 2013
Covering Letter		16 July 2013
Evidence of insurance or indemnity	KCL	01 August 2013
GP/Consultant Information Sheets	Patients Phases 1-III v:1	16 July 2013

GP/Consultant Information Sheets	Carers phase II v:1	16 July 2013
Investigator CV	Professor Irene Higginson	12 July 2013
Letter from Statistician	Letter from Dr Wei Gao, KCL	04 June 2013
Other: Myeloma UK grant award letter		08 January 2010
Other: Letter from funder St Christopher's Hospice		20 May 2011
Participant Consent Form: Phase I-Pilot QOL Survey	2	07 November 2013
Participant Consent Form: Phase II-Longitudinal QOL Survey Carer Version	2	07 November 2013
Participant Consent Form: Phase II-Longitudinal QOL Survey Patient Version	2	07 November 2013
Participant Consent Form: Phase III - Patient Focus Group	2	07 November 2013
Participant Consent Form: Phase III - Clinical Focus Group	2	07 November 2013
Participant Information Sheet: Phase I-Pilot QOL Survey	2	07 November 2013
Participant Information Sheet: Phase II-Longitudinal QOL Survey Carer Version	2	07 November 2013
Participant Information Sheet: Phase II-Longitudinal QOL Survey Patient Version	2	07 November 2013
Participant Information Sheet: Phase III - Patient Focus Group	2	07 November 2013
Participant Information Sheet: Phase III - Clinical Focus Group	2	07 November 2013
Protocol	2	04 July 2013
Questionnaire: Client Services Receipt Inventory CSRI		
Questionnaire: Global Mastery Subscale (Pearlin, 1981)		
Questionnaire: EORTC QLQ C30		
Questionnaire: EORTC QLQ MY20		
Questionnaire: Hospital Anxiety and Depression Scale (HADS)		
Questionnaire: Patient EQ-5D-3L		
Questionnaire: Zarit Burden Interview Short Form 12		
Questionnaire: Patient Outcome Scale Carer	2	
Questionnaire: Carer EQ-5D-3L		
Questionnaire: Myeloma-specific quality of life MYPOS	3	
Questionnaire: Data collection form for patients	1	16 July 2013
Questionnaire: Data collection form for carers	1	16 July 2013
Questionnaire: Data collection form for clinicians (phase III focus group)	1	16 July 2013
Questionnaire: Data collection for non-participants	1	16 July 2013
REC application		16 July 2013
Referees or other scientific critique report	Synopsis of peer review comments - response from applicants	26 November 2009
Response to Request for Further Information		07 November 2013

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

Further information is available at National Research Ethics Service website > After Review

13/LO/1140	Please quote this number on all correspondence

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

With the Committee's best wishes for the success of this project.

Yours sincerely

Dr Andrew Hilson
Chair

Email:nrescommittee.london-central@nhs.net

Enclosures: "After ethical review – guidance for researchers"

Copy to: *Keith Brennan, King's College London*

School of Medicine
at Guy's, King's College and St Thomas' Hospitals

Department of Palliative Care, Policy & Rehabilitation

Professor Irene Higginson
BMedSci BMBS FFPHM PhD FRCP
Head of Department
Professor Lynne Turner-Stokes
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KING'S College LONDON

Christina Ramsenthaler
Researcher
Cicely Saunders Institute
Bessemer Road
London SE5 9PJ

FAO: Noel Graham

National Research Ethics Service (NRES)
3rd Floor, Barlow House
4 Minshull Street
Manchester
M1 3DZ

30th April 2014

Dear Noel Graham,

Re: Longitudinal Quality of life in multiple myeloma, REC Ref: 13/LO/1140

The above study was approved by the Central London REC on 9th November 2013. I am writing to inform you of a non-substantial amendment.

We are about to open phase II of the study, which involves giving participants a selection of quality of life and other questionnaires that they fill in every 2 months, 5 times in total. The questionnaires have been approved by the REC in November 2013. To keep burden to a minimum for participating patients and their family member, we will not give all approved questionnaires at all times.

By combining these questionnaires into booklets, we have prepared 6 questionnaire booklets for use in our two participant groups (5 for patients with multiple myeloma and 1 for their family member). We have standardised the layout and formatting of the questionnaires throughout the booklets for clarity. The piloting of the questionnaires in phase I of our research has also prompted us to make minor changes to the time frames that questionnaires ask about (4 months instead of 3 months).

In addition, we have made a change to the questionnaire that asks about demographic details for patient participants. We have taken out one question (about the current/previous occupation) and would like to add one question about any other illnesses the participant might have.

This has been discussed with Will Bowen (R+D, King's College Hospital) and Keith Brennan (Sponsor and Director of Research Management, King's College London), who agree that this constitutes a minor amendment.

In enclose the following revised documents for your information:

- Questionnaire booklet for patients, time point 1 (Version 1, 14/4/2014)
- Questionnaire booklet for patients, time point 2 (Version 1, 14/4/2014)

- Questionnaire booklet for patients, time point 3 (Version 1, 14/4/2014)
- Questionnaire booklet for patients, time point 4 (Version 1, 14/4/2014)
- Questionnaire booklet for patients, time point 5 (Version 1, 14/4/2014)
- Questionnaire booklet for family members (Version 1, 14/4/2014)
- Demographic data collection form – patients (Version 2, 16/4/2014)

I would be grateful if you could acknowledge receipt of these new documents at you earliest convenience, so that King's College Hospital R+D unit can upload them onto the CSP for use by our collaborators.

Also, Simon Connolly from the South London CLRN also asked us to draw attention to the documents that have been approved by the REC in the Favourable opinion letter from 13/11/2013. In the list of approved documents both versions 1 of the participant consent form and participant information sheet for all three phases (which were the initial version before REC review) and versions 2 of these documents (version with requested changes made by the ethics committee). Could I please ask you to re-issue that letter with approval for version 1 of these documents removed. Otherwise there will be confusion for our collaborating centres which version to use.

Documents that need to be removed from the list of approved documents are:

- Participant Consent Form: Phase 1 – Pilot QOL Survey, Version 1, 16 July 2013
- Participant Consent Form: Phase II – Longitudinal Survey Patient, Version 1, 16 July 2013
- Participant Consent Form: Phase II – Longitudinal Survey Carer, Version 1, 16 July 2013
- Participant Consent Form: Phase III – Patient focus group, Version 1, 16 July 2013
- Participant Consent Form: Phase III – Clinician focus group, Version 1, 16 July 2013
- Participant Information Sheet: Phase 1 – Pilot QOL Survey, Version 1, 16 July 2013
- Participant Information Sheet: Phase II – Longitudinal QOL Survey Patient, Version 1, 16 July 2013
- Participant Information Sheet: Phase II – Longitudinal QOL Survey Carer, Version 1, 16 July 2013
- Participant Information Sheet: Phase III – Patient focus group, Version 1, 16 July 2013
- Participant Information Sheet: Phase III – Clinician focus group, Version 1, 16 July 2013

I would be grateful if you could remove these versions 1 from the list of approved documents, so that only version 2 of these documents has approval.

Thank you very much.

Yours Sincerely

Christina Ramsenthaler
Department of Palliative Care, Policy and Rehabilitation
King's College London

Cc: Professor Irene Higginson, Chief Investigator and Head of Department of Palliative Care, Policy and Rehabilitation, Cicely Saunders Institute, King's College London, Bessemer Road, London, SE5 9PJ.

NHS
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15 May 2014

Professor Irene Higginson
Professor and Head of Department
King's College London
Dept Pall Care, Policy and Rehab
Cicely Saunders Institute
Bessemer Road Denmark Hill London
SE5 9PJ

Dear Professor Higginson

Study title:	**Quality of life in multiple myeloma (MyCare): Longitudinal experience and potential use of information on quality of life for patient self-monitoring and patient care**
REC reference:	**13/LO/1140**
Amendment number:	**1**
Amendment date:	**06 May 2014**
IRAS project ID:	**129254**

- Combing questionnaires into 6 booklets
- Change to time frame that the questionnaire ask about, increased to 4 months
- Changes to demographic questionnaire

Thank you for your letter of 06 May 2014, notifying the Committee of the above amendment.

The Committee does not consider this to be a "substantial amendment" as defined in the Standard Operating Procedures for Research Ethics Committees. The amendment does not therefore require an ethical opinion from the Committee and may be implemented immediately, provided that it does not affect the approval for the research given by the R&D office for the relevant NHS care organisation.

Documents received

The documents received were as follows:

Document	Version	Date
Questionnaire: Questionnaire booklet for patients time point 1	1	14 April 2014
Notification of a Minor Amendment	1	06 May 2014
Questionnaire: Questionnaire booklet for patients time point 2	1	14 April 2014
Questionnaire: Questionnaire booklet for patients time point 5	1	14 April 2014
Covering Letter		16 April 2014

Questionnaire: Questionnaire booklet for patients time point 4	1	14 April 2014
Questionnaire: Demographic data Collection Form	2	16 April 2014
Questionnaire: Questionnaire booklet for patients time point 3	1	14 April 2014
Questionnaire: Questionnaire booklet for family members	1	14 April 2014

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

13/LO/1140:	**Please quote this number on all correspondence**

Yours sincerely

Anna Bannister
REC Assistant

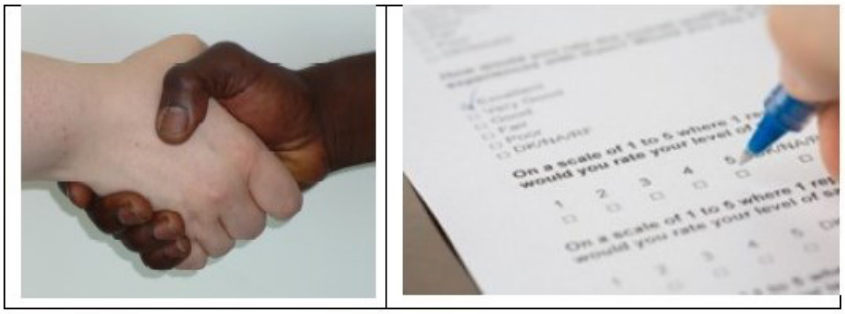
E-mail: nrescommittee.london-central@nhs.net

Copy to: *Keith Brennan, King's College London*

11 Appendix B: Protocol for the study

Protocol for ethics:

Quality of life in multiple myeloma (MyCare): Longitudinal experience and potential use of information on quality of life for patient self-monitoring and patient care



Investigators/Researchers

Christina Ramsenthaler, Research assistant, Department of Palliative Care, Policy and Rehabilitation, King's College London
Professor Irene J Higginson, Professor of Palliative Care and Policy, King's College London
Professor Richard Siegert, University of Auckland
Dr Gao Wei, Cicely Saunders Institute, King's College London
Dr Steve Schey, Consultant Haematologist and Lead of Myeloma Services, King's College Hospital NHS Trust.

Contacts

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Name and address of co-investigator: Christina Ramsenthaler
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Email: christina.ramsenthaler@kcl.ac.uk

Contents

1. Background

Multiple myeloma is an incurable cancer of the bone marrow (Bataille & Harousseau, 1997). It is the second most common haematological malignancy, with an incidence of 3.29 to 4.82 per 100,000 (Phekoo et al., 2004; 2006). The disease is more common among older age groups and thus is ever increasing with the ageing of the population. The clinical picture of myeloma is complex, including painful destruction of the bones, renal failure and bone marrow failure, coupled with the symptoms associated with bone marrow transplantation, chemotherapy and other forms of treatment (Bataille & Harousseau, 1997; Kyle & Rajkumar, 2008).

The treatment of myeloma has improved in recent years with the routine use of high dose chemotherapy and autologous bone marrow transplantation. These approaches have prolonged median survival to about 5 years for those under the age of 65. But data also show that only about one third of people with myeloma will survive these five years (Kumar et al., 2008; Phekoo et al., 2006). For those over the age of 65 survival is much shorter (median: 18 months), largely due to the fact that first-line treatments such as bone marrow transplantation are not available for this age group (Engelhardt et al., 2010). Overall, despite myeloma being a disease that cannot be cured, survival has improved in recent years (Kumar et al., 2008). Alongside this improvement has emerged a greater need to understand and improve the quality of life (QoL) of people with myeloma throughout the whole disease trajectory, including the phases in which people do not receive treatment or receive maintenance treatment only.

With the new treatment options available, people with myeloma now survive much longer with symptoms of the disease and the physical impairment that can result from it, and side effects and long-term effects of treatment. There is some evidence that people with myeloma have more symptoms and problems than those with other haematological cancers (Johnsen et al., 2009). A survey of 470 haematological cancer patients in Denmark included 54 myeloma patients which reported an average of 5.6 symptoms, of which 2.3 were reported as severe symptoms. Of all haematological patients, patients with myeloma reported the highest levels of pain, fatigue or weakness and constipation, as well as problems with role, physical and social function as well as financial difficulties (Johnsen et al., 2009). Those studies that have examined how health-related quality of life develops over time indicate that quality of life seems to be seriously compromised, even before people receive treatment (Sherman et al., 2009). After transplantation, some symptoms like pain improve, but some problems like depression

and life satisfaction worsened (Sherman et al., 2009). Health-related quality of life can also be a predictor for survival. Dubois et al. (2006) established that survival in relapsed patients can not only be predicted by clinical parameters (such as serum albumin or the presence of neuropathy), but also by physical quality of life and symptom scores (i.e. fatigue). This predictive power can also be shown in newly diagnosed patients with myeloma. Psychosocial quality of life was found to be a predictive of overall survival in one study (Strasser-Weippl & Ludwig, 2008).

These studies demonstrate the profound impact that multiple myeloma has on quality of life, and the need to capture and quantify this impact more clearly. They indicate that many patients experience considerable supportive care needs even before they begin treatment and probably also after end of treatment and into remission. They also demonstrate that it is essential to know about the quality of life for myeloma patients so that treatments can be tailored to ameliorate symptoms, provide time without treatment and prolong life wherever possible.

To date, only a handful of studies have measured quality of life at several points in the disease trajectory (Andersson, Ahlberg, & Stockelberg, 2011; Dubois et al., 2006; Frick et al., 2004; Frodin et al., 2011; Gulbrandsen et al., 2001; Sherman et al., 2004; 2009; Uyl-de Groot et al., 2005). These studies usually focus on people that participate in treatment studies of novel chemotherapeutical agents or that receive bone marrow transplantations. Most of these studies are cross-sectional in nature. Health-related quality of life is measured at one point in time, either before, during or after treatment (Frick et al., 2004; Gulbrandsen et al., 2001; Sherman et al., 2004; Uyl-de Groot et al., 2005). Follow-up after treatment has finished is usually limited, with two exceptions being studies by Sherman et al. (2009) and Frodin et al. (2011) which followed patients up for a longer time period of up to three years. Moreover, not all people with myeloma are eligible for these treatments and thus, results from these studies are not representative for all patients with myeloma as highly selected groups are included. The fact that psychosocial quality of life and not symptoms or physical status alone can predict survival (Strasser-Weippl & Ludwig, 2008) shows furthermore the need to measure quality of life in its multidimensionality. It would be worthwhile to explore other psychosocial predictors such as depression and anxiety.

Moreover, no study to date has specifically looked at the impact that the advanced stages of the disease might have on people's well-being and needs. Palliative care is currently not involved as a discipline in the care of these patients, despite the high symptom burden these patients experience during and after

treatment (Johnsen et al., 2009; Sherman et al., 2009). Haematological patients in general receive specialist palliative care less frequently than other cancer patients (Howell et al., 2010; 2011). One barrier to the integration of services is the unpredictability of the illness trajectory which renders prognostication difficult. A review has identified several areas of future research which need to be addressed in order to enhance palliative care provision for haematological patients (Manitta et al., 2010). The recommendations focus on the description of symptom patterns and distress as well as on needs and quality of life over time (Manitta et al., 2010). Information on the longitudinal course of symptoms, problems and concerns is therefore important for adequately planning service and care provision (Murray & Sheikh, 2008). A longitudinal study could identify predictors for poor quality of life in people with advanced stages of the disease and could therefore predict prominent problems to which services should respond. Also, it could provide insight into the processes utilised to maintain or improve quality of life throughout the disease trajectory, which in turn could be used to explore interventions for supporting quality of life in people with multiple myeloma (Molassiotis et al., 2011a,b; Potrata et al., 2011; Tierney et al., 2007). Periods of high burden and needs in people with multiple myeloma could be identified and thus provide insight when support by services is needed.

Not only could the information from the longitudinal study help identify which symptoms and problems best predict the quality of life experience and the resource use in people with myeloma. It could also help explore how questionnaires on quality of life could be used for routine assessment. People with multiple myeloma could then self-monitor the changes in their symptoms and problems and receive feedback on how to seek help for the problems that were identified. This would aid patient empowerment (Greenhalgh, 2009). Although recent years have seen a huge increase in the development and incorporation of health-related quality of life measures in research, these measures have been mainly used in studying the efficacy of treatments and health services. In recent years, quality of life measures have also been increasingly used in routine clinical practice (Detmar et al., 2002). Detmar & Aaronsson (1998) proposed that these measures be used to monitor disease progression and/or therapeutic response, to improve care, and to screen for physical or psychosocial problems. In the clinical trials that evaluated the use of PROs in clinical practice the main focus was on presenting information on quality of life to the doctor or nurse alone (Espallargues, Valderas, & Alonso, 2000; Gilbody et al., 2003; Greenhalgh & Meadows, 1999; Valderas et al., 2008). The trials showed a limited impact on communication between patients and clinicians. Moreover, results from the quality of life assessments were not always fed back to the patients, nor were patients able to access their

questionnaires. This shortcoming has been addressed in some studies that examined the effects of routine self-monitoring on patients with lung cancer, prostate cancer or cancer survivors (Mills et al., 2009; Snyder et al., 2009; Vickers et al., 2010). Self-monitoring was also used to track side effects of chemotherapy (Basch et al., 2005, 2007). Some of these studies demonstrated clinical usefulness, but problems with appropriate feedback to make information from QoL questionnaires meaningful to patients were identified (Mills et al., 2009; Snyder et al., 2009). Also, no study presented a specific rationale for choosing items for self-monitoring. A variety of formats were used - like paper diary forms, tablet PCs and online, web-based systems. It is not clear which format is preferred by patients.

The focus of routine assessment is different in terms of quality criteria that questions and items need to fulfill. McHorney & Tarlov (1995) postulated that measures used for routine assessment should focus on reliably and validly measuring intra-individual changes instead of group-level changes. They advocate high construct validity, high reliability, high clinical impact, enhanced sensitivity to change and brevity as the criteria that measures need to fulfil in order to be useful for frequent self-monitoring of QoL (McHorney & Tarlov, 1995). Currently, there exists no questionnaire that has been specifically developed to be used in routine clinical assessment in patients with multiple myeloma (Osborne et al., 2012). It is further unknown which other variables that predict health-related QoL trajectories and further health outcomes would be suitable for self-monitoring in this patient group and what their psychometric characteristics are. Moreover, the administration of these questions in different formats, together with presentation of interpretation aids, has not been explored. Therefore, these gaps in the evidence will be explored in the current study. It will be investigated which questions are the most suited for self-monitoring and how information on these assessments and the results should best be fed back to people with multiple myeloma and their clinicians.

The present study builds on a programme of research to develop and validate an instrument to measure the health-related quality of life of people with multiple myeloma (the MyQoL) (Osborne et al., 2012; REC reference number: 10/H0808/133). Also, the department has run several longitudinal studies of symptoms and quality of life in diverse patient groups, such as lung cancer and COPD patients (Bausewein et al., 2010a,b), end-stage renal disease(Murtagh et al., 2010, 2011a,b), Parkinson's disease (Higginson et al., 2012), and multiple sclerosis (Edmonds et al., 2007ab; Higginson et al., 2006).

2. Study aim and objectives

2.1 Aim

The primary aim of this study is to describe, understand and compare the individual quality of life of people with multiple myeloma over time and to explore the utility and acceptability of routine monitoring of quality of life.

2.2 Study objectives

(1) To evaluate the longitudinal changes in health-related QoL in multiple myeloma

(2) To describe the associations between individual level-changes and patient- and treatment-related factors that impact on health-related QoL and outcome variables in this group, in order to describe risk factors for poor QoL.

(3) To identify distinct subgroups (or 'phenotypes') of health-related QoL trajectories, based on changes over time, and to identify predictors for the subgroup membership of each individual.

(4) To identify the items and subscales that are the most reliable for monitoring of intra-individual changes within the three distinct groups of patients (patients newly diagnosed on first- or second-line treatment, patients with stable disease post-treatment or on maintenance treatment, and relapsed patients or patients with progressive disease), respectively.

(5) To examine which items or subscales have the best predictive validity in predicting low quality of life and health care utilisation and cost.

(6)To examine which items or subscales show the best longitudinal validity and sensitivity to change over time and in the three different subgroups of patients.

(7) To measure the impact routine assessment of health-related QoL might have on patient's self-efficacy and perceived control/mastery.

(8) To explore patients' and clinician's views on routine self-monitoring of health-related QoL in this patient group and to explore which data presentation formats and interpretation aids (decision aids or educational aids, population reference values, descriptive summaries of the health status of individuals with similar scores) are preferred by patients.

(9) To understand the burden that caring for a patient with multiple myeloma places on the primary caregiver.

3. Study design

The study is a prospective observational, multi-centre study, using mixed methods, in which patients with multiple myeloma are sampled concomitantly at different points in their disease trajectory. Participants will be approached for participation when they have been newly diagnosed with multiple myeloma, during the stable phase of their disease or during the phase of progressive or relapsed disease. Patients and their caregivers will be followed up over a period of 8 months or until death and asked to fill in questionnaires regularly every 2 months during that time.

The longitudinal nature of the study offers the opportunity to not only monitor quality of life and related issues over time, but also to explore the potential of frequent patient-led self-monitoring of health-related QoL. For this, a qualitative component, consisting of focus groups with patients and with health care professionals working in haematology, will be embedded in this study. Patients will also be asked to answer open questions in one of the questionnaires to explore whether frequent self-monitoring of quality of life is feasible, and what feedback layouts and interpretation aids are acceptable to patients and clinicians.

Phases

The study consists of three phases:

1) Pilot testing of methods

The questionnaires chosen for this study and the self-developed open questions on acceptability of self-monitoring will be piloted and further refined in a small study using brief discussion and cognitive interviewing with the first five consecutively sampled patients. Patients will be shown the questionnaires and asked whether they think that questions work and are clearly understandable. This will be achieved by cognitive interviewing. Cognitive interviewing is a technique that uses verbalisation to access the thoughts and feelings, and to understand ideas and interpretations of questions and questionnaires (Willis, 2005). It is a suitable technique for pre-testing survey instruments (Collins, 2003; McColl, Meadows, & Barofsky, 2003; Prior et al., 2011) and has been used in quality of life research and

with symptom questionnaires (Bergh et al., 2011; Murtagh, Addington-Hall, & Higginson, 2007). Questionnaires that have been validated in this population or with older people (such as the European Organization for Research and Treatment of Cancer QLQ-C30) (Osborne et al., 2012) will not be subjected to full cognitive interviewing, because they already have been shown to work for people with multiple myeloma. However, they will be piloted alongside questionnaires like the MyPOS to explore acceptability and time to complete as well as overall research burden.

2) Longitudinal survey of quality of life and related issues in patients with multiple myeloma and their main carers.

The longitudinal study will recruit patients and their carers over a period of 7 months and follow them up over 8 months. Data will be collected every 2 months for patients with multiple myeloma and every four months for caregivers. A variety of questionnaires will be used, asking patients and their carers about quality of life, symptoms, anxiety and depression, the amount of control they perceive to have over the disease, and the health care services they have received. Demographic and clinical variables will also be collected. They will also be asked about how feasible and useful they would find frequent self-monitoring of quality of life.

3) Focus groups

Focus groups with patients and health care professionals from the field of haematology will be run to explore the feasibility of routine self-monitoring for patients with multiple myeloma.

3.1 Overview of design

Quantitative data collection

Prospective quantitative data collection will take place at bi-monthly intervals (or at monthly intervals for patients with progressive disease as identified through the patient notes).

Quantitative data collection for patients with multiple myeloma: Baseline data collection will be face-to-face. The questionnaire pack consisting of questionnaires about demographics, quality of life, functional status, psychological distress and mastery will be administered after patients are consented by the researcher or the research nurse. If patients wish they can also take the questionnaire pack home and then post the questionnaires back to the department in a pre-stamped envelope. At later time points, patients will also be asked to fill in questionnaires about service use. Patients will receive telephone calls before subsequent follow-up time points. If patients are going to visit the outpatient clinic or the hospice, they will be asked to fill in the questionnaire pack then. If patients wish to fill in the questionnaire themselves at home, they will receive the questionnaire pack by post. It will be offered to them that they fill in the questionnaire with the help of the researcher or research nurse over the phone. The number of questionnaires to fill in will change from time point to time point, to minimise burden for patients (see 'Measures for data collection').

Quantitative data collection for caregivers of patients with mutliple myeloma:

The patient will be asked to identify the main caregiver. This can be a family member or significant other who is involved on a regular basis in caring for the patient, such as a spouse, partner, daughter, or son. The caregiver should have at least weekly contact with the patient. Caregivers will receive a separate questionnaire pack with measures of burden and quality of life. They will be asked to fill in the questionnaires at baseline and then every four months until the end of the study follow-up period. They will be offered the same support with filling in the questionnaires (phone contact or face-to-face interview) as the patients.

Qualitative data collection

Qualitative data will be collected (a) in the longitudinal survey in form of open questions, asked one time only, about the patient's views of the feasibility and acceptability of frequent self-monitoring of quality of life, and (b) in focus groups with clinicians and patients. The focus groups aim to explore patients' and

clinicians' views on routine self-monitoring of health-related quality of life and to explore which are the best ways of how to present this data to patients and clinicians so that they are able to interpret it. Focus groups will be held one time at about 3 months after baseline and patients will be recruited separately into them. The focus groups will complement the results from the quantitative survey by investigating whether frequent self-assessment of quality of life is feasible for patients, a question that cannot be answered by collecting data from questionnaires alone. A topic guide will be developed for the focus groups.

3.2 Study funding and approvals

This study is partly funded by Myeloma UK, a leading UK cancer organisation dealing specifically with myeloma and its related disorders, and partly funded by St Christopher's Hospice, London. The study will receive sponsorship from King's College London. Ethical and governance approvals for the study protocol will be sought through the Integrated Research Application System and approval for each site will also be sought from the Research & Development departments in the participating organisations. At present, recruitment will take place at three sites – King's College Hospital NHS Trust, the Guy's and St Thomas' NHS Hospital Trust and at St Christopher's Hospice, London. It is planned to open the study to two more centres in England, to be able to recruit a more diverse sample of myeloma patients at different stages in their disease trajectory.

3.3 Study setting

The study will be run from the Department of Palliative Care, Policy and Rehabilitation at King's College London. The multi-centre study will recruit patients from the following sites:

(1) Department of Haematological Medicine at King's College Hospital NHS Foundation Trust: This unit has the largest bone marrow transplant programme in the UK and performs more than 120 autologous, allogeneic and unrelated transplants a year of which around 40 are for people affected by multiple myeloma. The unit provides tertiary services for south-east England and other national and international centres. London and south east England include ethnically and socioeconomically diverse urban and rural areas.

(2) St Christopher's Hospice Palliative Home Care and Day Care Services: St Christopher's Hospice, Sydenham, is a large hospice with homecare, outpatient, and inpatient facilities serving five London Boroughs.

(3) Department of Haematological Medicine at Guy's and St Thomas's Hospital NHS Foundation Trust: This service offers inpatient and outpatient services. The department sees up to 10,000 outpatient visits of patients with diverse haematological conditions in the consultant-led clinics per year. The unit provides services for the south of London and also specialist services for patients from south-east England.

The study will be opened for two more sites with the aim to recruit a more diverse sample of patients with multiple myeloma than would be possible by recruiting from a tertiary centre or a hospice. We specifically aim to recruit patients that are not on active treatment or on maintenance treatment only and are in a stable phase of their disease. Inclusion of different settings, such as inpatient units, outpatient departments and palliative (home) care services will ensure that patients will be included that are at different stages in their disease trajectory - patients that are newly diagnosed, patients with stable disease and patients with relapsed or with progressive disease.

3.4 Study participants

Three groups of study participant will be recruited into this study:

a) Patients with multiple myeloma

Patients with multiple myeloma will participate in a longitudinal survey and answer questionnaires one to five times over a period of 8 months follow-up. In addition, patients will be recruited into a focus group that will be held one time.

b) Caregivers

The patient's main caregiver will be asked to participate in the study and fill in questionnaires one to three times over a period of 8 months follow-up.

c) Health care professionals

Health care professionals working in the field of haematology with experience in caring for patients with multiple myeloma will be asked to participate in a focus group that will be held one time.

a) <u>In-/exclusion criteria for patients</u>

Inclusion criteria

Participants will be eligible for study inclusion if they are:

(1) Over 18 years of age
(2) Have a confirmed diagnosis of multiple myeloma
(3) Have been told and are fully aware of the diagnosis
(4) Are English literate
(5) Have the capacity to give informed written consent to participate.

Exclusion criteria

The following exclusion criteria will be used in this study:

(1) Patients who are unable to provide informed consent.
(2) Patients who are too unwell, symptomatic, or distressed to participate - as judged by the clinical team
(3) Patients who do not speak English or are not able to read English.
(4) Patients for whom myeloma is not the most important health problem.

The eligibility criteria apply to all phases of the study.

b) Inclusion criteria for carers

Carers will be included if

(1) they are identified by the patient as the main caregiver (This can be a family member or significant other who is involved on a regular basis in caring for the patient, such as a spouse, partner, daughter, or son.),
(2) they are older than 18 years,
(3) they are aware of the diagnosis of the patient,
(4) are English literate and
(5) able to give informed written consent to participate.

c) Inclusion criteria for health care professionals

Health care professionals will be included if

(1) they are willing to participate,
(2) are able to give informed written consent to participate and
(3) have experience in caring for patients with multiple myeloma.

3.5 Study organisation and management

An advisory group is being formed for this study. The study research team and wider steering group includes expertise in psychosocial research, patient reported outcome measures, palliative care, haematology, data management, statistics and epidemiology, and psychometrics and measurement development. The conduct and progress of the study will be discussed and reviewed in regular meetings of the core research team and chief investigator, and also in regular meetings of the steering group. Patient reps. The study will be submitted for inclusion in the UK National Institute for Health Research (NIHR) Clinical Research Network Portfolio (CRN). Monthly, anonymised reports on study accrual will be sent to the CRN office. Six-monthly reports will be provided to the funder of the study.

3.6 Sampling

Phases 1 (Pilot testing of methods) and 2 (longitudinal survey of quality of life) will use consecutive sampling and include all patients that have been screened eligible and are willing to take part. All members of the available population will be considered for participation in the study. Phase 3 will use purposive sampling to capture the diversity of views across different age groups, gender, and disease stage. For focus groups with health care professionals, clinicians with a variety of professional backgrounds, clinical roles, and age groups will be sampled.

3.7 Identification and consent

Recruitment will be undertaken by oncology clinical care teams, at the participating NHS trusts and at St Christopher's Hospice, a non-NHS organisation. Dedicated research nurses funded by the National Institute of Health Research will undertake the recruitment in the participating centres. Eligible patients will be identified during discussions in routine multi-professional team meetings. The goal is to recruit patients during their face-to-face outpatient appointments with the myeloma care team. Each patient will be screened against the in-/exclusion criteria either by the clinician (nurse or doctor) caring for this patient. All eligible patients will be given a comprehensive information sheet containing the contact details of the study team and containing a description of the study and what participation entails for the patient, the voluntary nature of participation, patients' right to withdraw consent, at any time, without the need for explanation, and without their personal care being affected. Patients will be given 24 hours to consider whether they want to take part in the study. However, if potential participants indicate their willingness before that time period has passed, they will be allowed to take part. If participants are willing to participate, they will be asked to read, complete and sign a consent form. This will be signed

by the recruiting research nurse / researcher. A copy will be given to the patient and another copy will be filed in patients' medical notes (either hospital or hospice notes). The research team will retain the original signed consent form. Participants' General Practitioners will be sent a letter informing them of their patients' participation in the study if the patient indicates the wish that their general practitioner to be informed (on the consent form). The informal caregiver that is the main caregiver designated by the patient will only be approached if the patient has given his or her consent to do so. Written information will be provided to the carer and ample time will be given for the carer to consider the information before consent is being sought. They will be asked to give written informed consent once they have understood the benefits, risks and burdens associated with the study, had all information about the study and are aware that they can withdraw at any time without giving reasons.

Steps to prevent harm to participants

Participants will be advised they are under no obligation to take part. The purpose and intent of the work will be explained. Participants will be given the choice not to answer any particular question, whether in a focus group interview or when completing a questionnaire. They may skip the question and move on, return to the question later, omit the question altogether, or stop the interview or questionnaire. Patients will be made aware that they can withdraw from the study at any time, with no adverse implications for their clinical care.

Distress protocol

It is possible that participants may become distressed or raise issues during interviews which raise concerns or warrant a change in their medical management. Should this be the case, then a member of the research team will gain consent from the participant to discuss matters with the relevant member(s) of the multidisciplinary clinical care team, as appropriate. All of the research team will have completed Good Clinical Practice training and training on how to handle distress in research. The study includes a system for handling patients reporting abnormal result or indicating a clinically significant problem. The patient's clinical team will be notified of the results.

We anticipate distress to be infrequent and likely to reflect advanced disease. All questionnaires will be screened immediately following completion to check their content for any areas of clinical concern. This screening will be done at the site where the participant has been recruited. Screening will be carried out by a member of the clinical team nominated by the principal investigator at each site. If participants disclose any ideation of self harm or other risk to themselves or others, then this will be dealt with as an

urgent matter on discussion with the PI and a senior member of the treating medical team. Provision will be made to ensure the researchers have PI or senior back up available by phone whenever they are undertaking data collection.

3.8 Data collection

3.8.1 Phase I: Cognitive interviews

Data collection in phase I will consists of short qualitative, cognitive interviews with patients. They will be shown the questionnaires that will be used in the longitudinal survey and be asked about what they think of the questionnaires, using methodology for pretesting surveys (see Table 1) (Collins, 2003). The information from the cognitive interviews will be used to identify the cognitive processes as respondents answer the questions and to identify ways to improve and refine the questionnaires and the layout of the longitudinal survey.

Table 1. Questions for cognitive interviews

Aspect	Question
Comprehension	- What does the question mean to the respondent? - How easy or difficult is it to answer the question? - How would you change this question? (If problem)
Retrieval	- How well could you remember your experience when answering the questions? - How easy/difficult was it to think about the past [week] when answering the question? - Would there be a different time period that would be easier to understand?
Judgement	- What were you thinking about when you answered this question? - How did you arrive at your answer to that question? - Do you find any of the questions upsetting/embarrassing/inappropriate?
Response	- Was it hard or easy to select an answer from the options given? - Did all options make sense for this question?
Structure	- What do you think about the length of the questionnaire? - What do you think about the size of the text? - What do you think about the layout of the questionnaire? - What do you think about the response options and how they are displayed?
Appropriateness	- What do you think about the overall length of the survey? - Do you think that the survey is burdensome? - Would you like to fill out the questionnaire on your own or with the help of another person?

3.8.2 Phase II: Data collection in the longitudinal survey

In phase II, the longitudinal survey of quality of life, patients with multiple myeloma and their primary caregiver will be asked to fill in a set of questionnaires (detailed below, see section 'Measures') at several time points. Not all questionnaires will be filled in at all time points. How often and when questionnaires will be given to the patients and their carers is detailed in Table 2.

Table 2. Overview of longitudinal data collection

Time	Baseline	2 mos	4 mos	6 mos	8 mos
1) Patient					
Demographic questionnaire	x				
MyPOS	x	x	x	x	x
EORTC-QLQ-C30 and -MY20	x	x	x	x	x
EQ5D	x	x	x	x	x
HADS	x		x		x
Mastery subscale (Pearlin et al. 1981)	x		x		x
CSRI			x		x
2) Caregiver					
Demographic questionnaire	x				
Zarit-Burden Inventory Short Form 12	x		x		x
EQ5D-3L	x		x		x
Carer assessment of patient, using the Palliative Care Outcome Scale (POS) Carer Version 2.0	x		x		x

*MyPOS = myeloma-specific quality of life questionnaire, EORTC QLQ C30 and EORTC QLQ My20 = European Organization for Research and Treatment of Cancer Quality of life Questionnaires – Core Module 30 and Myeloma-specific Module20, EQ5D – 5L, HADS = Hospital Anxiety and Depression Scale, CSRI = Client Services Receipt Inventory

Measures

For patients:

a) Demographic and clinical data:

At baseline (study entry), the following demographic and clinical data will be collected from the patient and from the medical records (using both paper and electronic systems, depending on what is used in the participating centres):

- Age
- Gender
- Marital status
- Ethnicity
- Religion
- Educational level
- Occupation status and current occupation
- ECOG performance status
- Disease and treatment details, among them:
    - Date of diagnosis
    - Immunoglobulin type
    - ISS stage at diagnosis
    - Current phase of disease
    - Current treatment
    - Details of any other treatments in the past and the response obtained
    - Comorbidities: Charlson comorbidity index

Demographic and clinical data will be collected at baseline, together with the first set of questionnaires. Information from the medical records will be assessed at baseline to collect some of the clinical information (i.e. stage of disease, stage of myeloma) that cannot be asked of the patient. Details about the disease status, treatment and the response to treatment will also be extracted from the medical notes every two months when patients fill in the quality of life questionnaires in order to collect information on outcomes (i.e. response to treatment).

b) Quality of life questionnaires & psychological distress:

- **The MyPOS**: The MyPOS is a myeloma-specific, multidimensional instrument covering physical, psychosocial, and existential concerns, information needs and satisfaction with health care. It consists of one open question which asks patients to list their three main problems or concerns, then presents them with 11 symptoms that are frequently experienced by patients with multiple myeloma. There are 16 additional questions about their psychosocial wellbeing, other concerns and their satisfaction with care. Overall, the questionnaire consists of 29 items that are scored on a 5-point Likert scale from 0 to 4. It was developed as a questionnaire specifically for clinical use. It has been developed in the study *Quality of Life of People with Multiple Myeloma and Follicular Lymphoma* (REC reference number: 10/H0808/133). The questionnaire is currently validated in a large multi-center cross-sectional study.

- **The EuroQoL EQ-5D-5L**: The EQ-5D is a standardised generic health status questionnaire. It consists of two parts - the descriptive part with 5 dimensions (mobility, self care, usual activities, pain/discomfort, anxiety/depression) that are scored on a 5-point scale, ranging from no problems to extreme problems, and the visual analogue scale. The visual analogue scale scores the self-reported health of the respondent. Responses to the five dimensions can be used to derive health utilities (preferences for different health states) which can be used for the calculation of quality-adjusted life years for economic evaluations. The EQ-5D has been shown to be valid and reliable (Herdman et al., 2011; Rabin et al., 2011). The EQ-5D has been shown to be responsive to change in patients receiving haematopoietic stem cell transplantation (Uyl-de Groot et al., 2005) and in patients with multiple myeloma of different disease stages and receiving different treatments (Kvam, Fayers, & Wisloff, 2011).

- **The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ) - Core 30 and Myeloma Module MY 20**: The EORTC-QLQ-MY 20 consists of a generic health status questionnaire, the EORTC-QLQ-C30 (version 3), and the disease-specific component MY20. The EORTC-QLQ-C30 contains 30 items which include five functional scales (physical, role, cognitive, emotional and social), three symptom scales (fatigue, nausea/vomiting and pain) and six individual items (other symptoms, financial difficulties and global quality of life)(Aaronson et al., 1993). The MY-20 is a myeloma-specific module for the QLQ-C30 and consists of 20 items which are scored on four independent subscales: two functional scales (body image and future perspective) and two symptom scales (disease symptoms and side effects of treatment). All items are scored on a 4-point Likert ranging from 'not at all' to 'very much' (Cocks et al., 2007; Stead et al., 1999). Each scale is converted to a range from 0-100. For the functional scales and the global quality of life scale, higher scores represent a better health state, whereas for the symptom items/scales, lower scores represent a better health state. Both questionnaires have been extensively validated in patients with myeloma at different disease stages and with different treatments. They have been shown to be reliable, valid, responsive and acceptable in this group (Osborne et al., 2012).

- **The Mastery Scale** (Pearlin et al., 1981): To measure the impact of the disease and the treatment on the perception of self, perceived control/mastery will be measured, which measures the extent to which individuals they have personal control over what is currently happening in their lives and what is likely to happen in the future.

- **The Hospital Anxiety and Depression Scale (HADS)**: The HADS is a questionnaire designed for use in non-psychiatric hospital settings to assess psychological distress. The HADS consists of 14 items, seven items each for anxiety and depression, which are scored on a 4-point Likert scale ranging from 0 (no problem) to 3 (maximum distress). The total score ranges from 0 to 21. Cut-offs for the presence of clinically relevant anxiety or depressive disorder have been established with the cut-off of 11 of 21 points showing the best sensitivity and specificity (Herrmann, 1997; Snaith, 2003; Zigmond & Snaith, 1983).

c) Outcome measure: Health care utilisation and costs

- **Adapted version of the Client Service Receipt Inventory (CSRI)**: The CSRI provides information about service utilisation by collecting retrospective information about the services received. The questionnaire is designed to be filled in by the person receiving the services, administered by the interview. For reach service type, the number and average duration of contacts is recorded. This information can be used to demonstrate the variety of services used and how resources are allocated. It is a validated tool and has been used in range of research studies including in mental health, community care of older people and dementia (Beecham & Knapp, 1992; Chisholm et al., 2000; Schneider et al., 2002). The CSRI will be used in this study to calculate costs by combining service use data with unit cost information. Costs to patients and carers will be estimated.

For caregivers:

a) Demographic questionnaire

At baseline (study entry), demographic data will be collected from the caregiver, including age, gender, ethnicity, religion, educational level and occupation status/current occupation.

b) The Zarit Burden Interview (ZBI) (Zarit, Orr, & Zarit, 1985; Zarit, Reever, & Bach-Peterson, 1980; Zarit & Zarit, 1990)

Caregivers will be asked to complete the Zarit Burden Interview, a 22-item questionnaire used widely to assess the level of burden experienced by the principal caregivers (Zarit et al., 1980, 1985; Zarit & Zarit, 1990). It contains fives scales: burden in the relationship (6 items), emotional well-being (7 items), social

and family life (4 items), finances (1 item), and loss of control over one's life (4 items). Responses are scored on a 5-point Likert scale, ranging from 0 (never) to 4 (always). The total range in score is 0-88. Cronbach's alpha for the Zarit Burden Interview was found to be 0.91 in one study (Picot, Youngblut, & Zeller, 1997).

c) Medical Outcomes Short Form – 12 tool (MOS-SF12) (Ware, Kosinski, & Keller, 1996)

The Medical Outcomes Short Form – 12 (MOS-SF12) is a shorter version of the MOS SF-36. It assesses 8 health concepts, limitations in physical, social, role activities because of health problems, general mental health and overall health in the past four weeks. The 12 items can be summarised to form to overall scales – the 'Physical component summary scale' and the 'Mental component summary scale'. It will be used to assess the health-related quality of life of caregivers. It has been validated extensively and population norms are available for an assessment of how the quality of life and burden of informal caregivers compare to the general population (Ware et al., 1995, 1996).

d) Palliative Care Outcome Scale (POS), Carer version

The Palliative Care Outcome Scale (POS) is a multidimensional questionnaire covering physical, psychosocial, spiritual, organisational and practical concerns. The POS consists of 11 items, scored on a 5-point Likert scale ranging from 0 'not at all' to 4 'overwhelmingly'. It has been validated in numerous populations (Hearn & Higginson, 1999). It asks caregivers to make an assessment of the physical, emotional, social and spiritual well-being of the patient.

Baseline and follow-up data collection

Baseline and follow-up data collection:

Data will then be collected prospectively over a period of 6 months onwards, to give a maximum of 6 time points for assessment (baseline and five follow-up assessments). In addition to the baseline assessment (T0), patients will be examined at bi-monthly intervals: at 1 months post baseline (T1), 2 months (T2), 3 months (T3), four months (4), and at five months (T5). Patients who have progressive disease will fill in the questionnaires at monthly intervals. Data will be collected via a postal questionnaire. At each time-point, patients will have up to two weeks to complete the survey. Before the survey is mailed to them, they will receive a telephone call to remind them of the questionnaire and

ask them to return it within the next two weeks. If patients do not send the questionnaire within the time frame, they will receive another reminder by phone. Questionnaires will be sent back to the Cicely Saunders Institute of Palliative Care in pre-stamped envelopes. The same process of data collection will be used for the carer of the patient. Contact by telephone was mentioned as the preferred method of contact for data collection in a study by Shipman et al. (2008).

Data collection on non-participants

Recruitment of potential eligible patients aims to be as complete as possible. However, it is anticipated that not all eligible patients that are approached will want to take part in the study. To estimate the amount of selection bias, we will collect aggregate-level data on non-participants (age, gender, disease status). This will be done via an audit of all patients under the service in the year the study was run.

3.8.3 Phase III: Focus groups with patients and health care professionals

Focus groups with patients and health care professionals from the field of haematology will be run to explore the feasibility of routine self-monitoring for patients with multiple myeloma. Focus group discussion will be guided by a topic guide that will be developed on the basis of a systematic review.

3.9 Data analysis

Phase 1: Piloting of methods

The questionnaires used in this study will be piloted by using cognitive interviewing in order to determine whether questions work as intended and to explore the acceptability and time to complete plus overall research burden. Interviews will be recorded and transcribed verbatim. Content analysis will be used for analysis (Barofsky, 2003; Collins, 2003; Murtagh et al., 2007; Willis, 2005).

Phase II Longitudinal survey

The questionnaires and demographic as well as clinical information will be described cross-sectionally and longitudinally. Descriptive statistics will use means and standard deviations (if continuous) and medians and interquartile ranges or counts (percentages) (if categorical). Numbers and proportions as well summary scores for items and scales will be reported. After univariate description and bivariate

analysis of differences and associations, multivariable analysis will be run to examine subgroups of quality of life experience and risk factors or predictive factors for the outcomes selected in this study. Longitudinal analysis of data will focus on modelling within-person trajectories and between-person comparison of subgroups. The group trajectories for the total scores and for individual subscales will be plotted. Multivariable analysis will use ANOVA with post-hoc tests and multiple regression techniques, were appropriate. If distributions and skewness of data indicate that data is not normally distributed, the appropriate non-parametric statistical techniques will be used (for example the Wilcoxon test for paired differences). As the EORTC-QLQ-C30 offers the opportunity to compare the results to a norm population (Osoba, 2007; Osoba et al., 1998), comparisons will be made cross-sectionally and longitudinally for that measure. Minimal clinically important differences have been suggested for the EORTC-QLQ-C30 and the HADS and these thresholds will be used in the analysis. A survival analysis using multivariate methods will be run, as appropriate.

For reliability and psychometric analyses (objectives 4 and 6), standard reliability tests (Cronbach's alpha and test-retest reliability), test of construct validity and tests of sensitivity to change (comparing subgroups on treatment over time versus a stable subgroup of patients not on treatment) will be performed. Psychometric analyses will use techniques from classical test theory as well as modern item response theory (Rasch analysis). Statistical analyses will be run using programmes like SPSS and the computational package R. Psychometric analyses will also use RUMM, a programme specifically designed for item response theory.

Missing data will be imputed using various methods and sensitivity analyses will be run to check the influence different methods of imputation have on the results.

Quantitative and qualitative data from this study might be re-analysed in a secondary analysis by the researchers involved in this project or by researchers working with and supervised by Professor Irene Higginson, the chief investigator of this study.

Phase III: Focus groups

Qualitative data from focus groups and from open questions in the questionnaires will be tape recorded and/or transcribed and analysed using content analysis to identify themes, and framework analysis used to contrast themes in different subgroups. As questions that will be discussed in focus groups or answered in open-ended form in the questionnaires will be focused on acceptability and feasibility of

self-monitoring of quality of life and not on experiences of illness, content and framework analysis are better suited than more interpretative analysis techniques to summarise the data and highlight differences in attitudes and perceptions of respondents. NVivo, a software to support qualitative analysis, will be used. To reduce bias in the analysis, a sample of the coded data will be cross-checked by another member of the research team or another researcher supervised by the CI (Professor Irene Higginson) within the Department of Palliative Care, Policy and Rehabilitation.

3.9.1 Sample size calculation

The main part of this study is phase II, the longitudinal study. The sample size estimation for the longitudinal study is detailed below.

Phase I, which comprises the pilot testing of methods, will recruit 5 patients. As this phase is concerned with pre-testing of methods, a small sample is needed (Collins, 2003).

Phase II, the longitudinal study, will recruit 86-90 patients (see sample size calculation below).

Phase III, which comprises two focus groups - one with patients and one with health care professionals - will recruit 8-10 participants per focus group for a total of 16-20 participants. There are no concrete guidelines for sample size in qualitative research (Guest, Bunce, & Johnson, 2006). Sampling should continue until saturation of codes in the thematic content analysis is reached. Sampling will be purposive in order to represent relevant population diversity according to specific demographic and clinical characteristics (age, gender, ethnicity, disease stage). A sample size of 20 participants has proved sufficient to obtain saturation of themes in the qualitative interviews that were undertaken in the cross-sectional study on quality of life in multiple myeloma (Osborne, Ramsenthaler, & Higginson, 2012). The sample size in the focus group was also based on recommendations in the literature (Barbour, 2008; Brod, Tesler, & Christensen, 2009; Krueger & Casey, 2010; Morgan, 1997). Sample sizes in qualitative studies usually depend on achieving saturation of themes - as determined in the field. Based on previous experience we envisage that sample sizes of 20 participants will be sufficient and we will keep this under review during the study (Barbour, 2008; Brod et al., 2009; Krueger & Casey, 2010; Morgan, 1997).

The sample size was decided upon by calculating a sample size estimate for a longitudinal study. As one of the study's main objectives is to identify distinct subgroups of health-related quality of life and identify predictors for the subgroup membership of each individual, it is important to power for detecting these subgroup differences over time.

Sample size calculation for 'within person' studies to detect changes over time was calculated using the programme GPower 3.1 (Faul et al., 2007, 2009). The estimation could not be based on the calculation of a standardised difference that is recommended by Altman (1991) as it was not possible to obtain an estimate of the standard deviation of changes as longitudinal studies of persons with multiple myeloma that used the EORTC-QLQ-C30 to measure quality of life over time (Andersson et al., 2011; Sherman et al., 2009). These studies only reported means and standard deviations at different time points, but not mean change and standard deviation of the changes. However, effect sizes of changes of health-related quality of life over time could be calculated from this data. The effect size was estimated from the study by Andersson and co-authors (2011). They compared changes in global quality of life and in the subscales as measured by the EORTC-QLQ-C30 between subgroups of patients with multiple myeloma, receiving either autologous or allogeneic stem cell transplantation, over one year. Comparison of global quality of life between subgroups showed pronounced differences between subgroups with an effect size of 0.6 (effect size (Hedges' g) was computed as mean global quality of life in the first subgroup subtracted by mean global quality of life in the second group and divided by the pooled standard deviations of both groups (Sutton et al., 2000)). A similar effect size for the within-subject changes over the period of 12 months was computed to power the within-subject comparison to detect changes over time based on the data presented in Andersson and co-author's (2011) study. The estimate of the effect size of within-subject changes ranged from 0.4 to 0.54.

a) Sample size calculation for detecting differences between subgroups

In order to detect a difference between subgroups in an independent, two-tailed t-test with 80% power, at a significance level of 5% and assuming a moderate effect size of 0.5-0.6 (see computation above), the estimated total sample size is 64 to 90.

b) Sample size calculation for detecting within-subject changes over time

In order to detect within-subject changes over time in a dependent, two-tailed t-test with 80% power, at a significance level of 5% and assuming a moderate effect size of 0.4-0.5 (see computation above), the estimated total sample size is 34 to 54 participants.

As the sample size estimations show, the calculation for detecting differences between subgroups shows the more conservative estimate. It will be used as the estimate of total sample size for this study.

Allowing for attrition of 25-30% over the course of one yea r(Steinhauser et al., 2006; Stromgren et al., 2005), this would mean that 113-117 patients need to be recruited to the study.

3.10 Data management and security

All personal data will be managed according to the principles established in the Data Protection Act 1998. All of the researcher will undertake and update her Good Clinical Practice Training, and current research governance processes will be followed. Completed questionnaires, demographics forms and interview transcripts will be anonymised using a unique study identification number and contain no patient identifiable data. The only place that the study identification number will be linked to the participant's name will be the consent form. Questionnaires, demographics forms and transcripts will be stored separately to the consent forms, each in a separate locked cabinet.

3.11 Dissemination

Participants will be invited to receive a feedback summary of the research once completed. For all participants, we will check on illness status with the participating site clinical team prior to feedback (some patients may have died in the interval between data collection and study outputs, and we will avoid distress to family in this way).

Results will be published as they emerge through the project. Information will be disseminated via (knowledge exchange seminar, conferences, papers in scientific journals).

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12 Appendix C: Ethical considerations in survey research

given at all time points.)				about the questionnaires. The survey will be completed in the participants' own home and returned by Freepost.
PHASE II: POSTAL QUESTIONNAIRE OF INFORMAL CARERS OF PATIENTS WITH MYELOMA (Questionnaire comprised of validated measures of subjective burden, health status and health of the patient. Not all measure	1-5	0	30-40 mins	The researcher, Christina Ramsenthaler, or any other researcher supervised by the CI (Prof Higginson) or the researcher's academic supervisors. Questionnaires will be sent to the participant via post. Participants will get support via telephone to address questions or concerns about the questionnaires. The survey will be completed in the participants' own home and returned by Freepost.
TELEPHONE CONTACT (To support completion of study questionnaire and to address any concerns from the participant, telephone contact will be made aroung delivery of questionnaires and during completion	1-5	0	5-10 mins	The researcher, Christina Ramsenthaler, or any other researcher supervised by the CI (Prof Higginson) or the researcher's academic supervisors.
PHASE III: FOCUS GROUP WITH PATIENTS WITH MYELOMA (Focus group will be held with 8-10 patients at the Cicely Saunders Institute at King's College London)	1	0	60-90 mins	The researcher, Christina Ramsenthaler, or any other researcher supervised by the CI (Prof Higginson) or the researcher's academic supervisors.
PHASE III: FOCUS GROUP WITH HEALTH CARE PROFESSIONALS (Focus group will be held with 8-10 clinicians at the Cicely Saunders Institute at King's College London)	1	0	60-90 mins	The researcher, Christina Ramsenthaler, or any other researcher supervised by the CI (Prof Higginson) or the researcher's academic supervisors.

A21. How long do you expect each participant to be in the study in total?

Median survival in this age group of those under 65 years is 42 months and 18 months in the group of patients aged 65 years or older (Phekoo et al. 2004).

Recruitment will continue for 7 months and follow-up will continue for 8 months - one year after recruitment ends. Patients will be followed-up for a maximum of 8 - 12 months after they gave consent to participate in the study, or until death. In the three phases of the research, different patients will participate. However, some participants might participate in more than one part of the research. For those that participate in multiple phases, the overall length of time in the study will not be longer than 12 months. For those participants that take part in phase I (pilot study) or in phase III (focus groups) only, the maximum participation time is 1 day.

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A22. What are the potential risks and burdens for research participants and how will you minimise them?

For all studies, describe any potential adverse effects, pain, discomfort, distress, intrusion, inconvenience or changes to lifestyle. Only describe risks or burdens that could occur as a result of participation in the research. Say what steps would be taken to minimise risks and burdens as far as possible.

The proposed study is expected to have minimal risk for participants. It does not involve invasive procedures or non-routine blood tests, it involves no novel therapeutic interventions with potential side-effects and the study questionnaire and interviews will be completed in a place of the participants own choosing at a time suitable to them. In addition, taking part will not affect participants' medical management in any way, and they will have the option of withdrawing from the study at any time.

Completion of questionnaires can be time-consuming. We aim to allow patients to participate in a way that is g§üj§¶´efòi ´§ ´liü, e¢h ®mòò §jji¶ jòi|mfmòm´} e¶§©¢h ´li ´müi e¢h •òegi §j ´li g§k¢m´m∑i m¢´i¶∑mi®™. Pe´mi¢´™ e¢h ´lim¶ informal caregivers will be able to complete the questionnaires in the longitudinal survey at home at a time convenient to them. If they become fatigued during the process of filling in the measures, they will be able to break and come back to them later. They will be able to return the questionnaires via Freepost to the institute, so that no extra costs are

accrued. If patients or carers need to travel to the institute for data collection they will be offered travel expenses.

Surveying and interviewing participants about experiences may include areas that may be potentially sensitive,

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College London, through extensive clinical and research experience with individuals with advanced disease and their families and carers, and has developed formal protocols for dealing with distress uncovered during research studies (please see section A23 and supporting documents for details of how we will address this). Whilst distress may be uncovered in some participants in studies such as this, there is a large body of evidence demonstrating the significant benefits to the participants in similar studies (please see section A24).

A23. Will interviews/ questionnaires or group discussions include topics that might be sensitive, embarrassing or upsetting, or is it possible that criminal or other disclosures requiring action could occur during the study?

(●) Yes ( ) No

If Yes, please give details of procedures in place to deal with these issues:

Interviewing patients or completion of QOL questionnaires may explore sensitive topics (Lee & Renzetti 1990, Keogh & Daly 2009). In order to manage the potential distress that might arise for participants in this study, we put several strategies in place. Participants will be given the choice not to answer any particular question, whether in an individual interview, focus groups, or when completing a questionnaire. They may skip the question and move on, return to the question later, omit the question altogether, or stop the interview / questionnaire altogether. Patients will be made aware that they can withdraw from the study at any time. There is also a distress protocol in place and researchers working on the project have training in palliative care and in counselling. We will also try to minimise burden for clinical staff at the participating sites.

Evidence suggests that – although some of the topics in the questionnaires (i.e. questions about future concerns and dying) can be perceived as sensitive and distressing -
things and were less distressed by these topics than expected (Alexander 2010, Takesaka et al. 2004, Casarett & Karlawish 2000). In general the risk of distress in descriptive studies has been found to be minimal, but self-reported distress varies widely among studies and depends on participant's characteristics (Casarett & Karlawish 2000). Distress was found to be more likely in younger respondents, in younger patients and in family members of cancer patients (Takesaka et al. 2004). Some of these groups might be included in this study. However, most patients and caregivers are willing to participate in research and experience benefit from it. For example, McGrath asked parents of children with haematological malignancies whether they perceived the research interview as distressing and participants indicated that they had been comfortable in discussing their circumstances (McGrath 2003). In a study by Emanuel et al. (2004), less than 5% of patients and caregivers reported distress from interviews that asked questions about symptoms, care needs and economic burdens, plans for terminal care, social support and communication with health care providers. More than 40% of them found answering questions in this survey somewhat or very helpful.

However, data also suggests that the risk of self-reported distress varies widely among studies and that characteristics of the participants influence how much distress is experienced (Casarett & Karlawish 2000). For example, some of the distress in this study might not be induced by asking about sensitive topics but because some participants might be filling in questionnaires during a time when they are distressed and anxious as a result of their situation (Beaver et al. 1999). Physical distress and fatigue may vary across the disease trajectory (Arraf et al. 2004). As participants are asked to fill in questionnaires in this study at various time points, these issues need to be taken into account. Participants will receive the questionnaires through the post and will be advised to fill them in at a time convenient to them. This will allow for a more flexible approach to data collection as participants can fill in the questionnaire when they want and are not too fatigued to do so (Barnett 2001, Shipman et al. 2008). This also allows them to take a break and returning to filling out the remainder at a later time (Shipman et al. 2008). Some participants might need help with filling out the questionnaires and this help will be provided if necessary, either over the telephone or in a face-to-face meeting (i.e. when participants come for their regular clinic appointment to the outpatient department). Participants will also receive a phone call before receiving the questionnaire. If participants appear to be severely physically distressed at the time of the phone call, consent will be asked to inform the clinical team and seeking symptom relief will take precedence. The methods of recruitment and data collection will also be pre-tested for appropriateness and acceptability in phase I of this research.

We have developed a distress protocol to be followed in the event that distress is caused by or identified during the study (see protocol). Also, potential participants will be informed in the patient information leaflet and during consenting that some of the questions might be perceived as upsetting. They will be reminded about the option to withdraw or not answering problematic questions and such a reminder will be included at the start of each questionnaire. However, questionnaire design will seek to engage the respondent as fully as possible in answering each item in order to enhance validity of the research (Evans et al. 2002). Participants will also be informed when consented that they might be asked permission to contact their healthcare team if they appear to be in distress.

The chief investigator (Professor Irene Higginson) and the principal investigators (Dr Polly Edmonds, Dr Nigel Sykes) are clinicians with specialist training in palliative medicine. The main researcher (Christina Ramsenthaler) is a clinical psychologist with clinical training in counselling and MSc-level training in palliative care. Any other researcher interviewing patients as part of the study will have previous experience interviewing in sensitive areas, have relevant university qualifications, and will by supervised by Professor Higginson.

It is possible that participants may raise issues during interviews which warrant a change in their medical management, or raise concerns about their mental health. Should this be the case, then a member of the research team will gain consent from the participant to discuss matters with the relevant member(s) of the clinical team, such as the treating haematologist or GP. All questionnaires will be reviewed to check content immediately following completion to allow screening for any such areas of concern.

If participants disclose any ideation of self harm or suicide then this will be dealt with as an urgent matter on discussion with the CI and a senior member of the treating medical team.

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A24. What is the potential for benefit to research participants?

There is a growing body of evidence describing perceived benefits of participating in research for patients with cancer and other life-limiting diseases. Research needs to balance risks and benefits. People with multiple myeloma and their family members can benefit from participating in this study. That benefits can be gained by participating in research was shown in a review that identified 100 articles outlining positive outcomes from research in vulnerable participants with only one article reporting any negative outcome (Alexander 2010). A similar high percentage of positive outcomes occurred in studies despite the warning that information would not be shared with the health care providers of participants and thus that taking part in research might not results in direct benefit. Despite this warning, gaining insight into values and opinions and being able to help others by answering questionnaires and providing information proved helpful to patients (Emanuel et al. 2004). There is potential for the research process to be therapeutic, cathartic and to help participants gain self-awareness and empowerment of having their voice heard and being able to access information (Gysels et al. 2008, Hutchinson et al. 1994, Orb et al. 2000, Reid 2009, Sorrell & Redmond 1995). Cancer patients with a life-limiting illness are equally willing to participate in research, be it clinical trials, observational or qualitative studies (Shipman et al.2008). As perceived benefits, greater attention and monitoring as well as contributing to other were named (Ling et al. 2000, Ross & Cornbleet 2003, Shipman et al. 2008). Denying patients an active role in research prevents them from contributing to knowledge about how to improve care for others (Lee & Kristjanson 2003).

One indirect benefit for participants is that research can enhance health care services (Agrawal & Danis 2000). The practice of medicine should rely on a sound evidence base (Sackett 2001, Boult et al. 2003) which allows a safe clinical and therapeutical practice of medicine. Dame Cicely Saunders emphasised the need for a wide evidence base and the importance of research in the care of people with life-limiting diseases (Addington-Hall 2003). Despite her efforts, this evidence base is still lacking in many parts of cancer care and palliative care (Field & Cassell 1997,

Higginson 1999, Mount et al. 1995). The need for a greater evidence base in these areas has become a national priority (Field & Cassell 1996, Alexander 2010). The demographic shift and an ageing population mean that more and more people will be dying from chronic or progressive illnesses and will have substantially greater care needs, not only at the end of life (Higginson 1999, Gysels et al. 2012). Not only will there be a substantial need for good quality care in the future, but already some groups lose out on palliative care and supportive care and are underserved (Higginson 1999). This is particularly true for individuals with multiple myeloma, a cancer that is often diagnosed late into the disease. Only a handful of studies have explored needs of people with multiple myeloma, but not in the later stages of disease (Sherman et al. 2009, Johnsen et al. 2009).
Knowledge and understanding should also be advanced in this group as unique needs may exist. To make sure that services meet the needs of individuals with multiple myeloma, service delivery should be based on epidemiological studies exploring the prevalence of symptoms and the interaction of problems in this patient group (Boult 2003, Jubb 2002). Findings from other cancer diseases or other clinical settings are not generalisable and cannot be extrapolated or transferred to multiple myeloma (Alexander 2010). The information is also necessary to enable patients to make autonomic choices about the treatment they receive and to anticipate which symptoms or problems they might encounter in the future (Keeley 2008). Therefore, one ethical justification for researching quality of life in multiple myeloma is that in the interest of justice and fairness, these people should not be excluded from research as it denies them the opportunity to contribute to the evidence base and it denies future patients the opportunity to make sound decisions about their care that are based on evidence from studies in patients with multiple myeloma (Koffman et al. 2009, Boult 2003, Field & Cassel 1997).

Moreover, specifically information on quality of life as one outcome on which decisions about provision of services and treatments (i.e. National Institute for Health and Clinical Excellence 2011) are based is necessary. Health policy makers and other stakeholders, as the patients themselves, focus on outcomes like costs and access to care, but also quality of life (Prince-Paul & Daly 2008). The Cancer Research UK programme now routinely collects quality of life (Ashley et al. 2012) in order to explore how physical, psychosocial and financial difficulties develop over time in people with cancer. Much is still unknown about the trajectory of quality of life over periods in which individuals with multiple myeloma do not receive active treatment or maintenance treatment only, and into the later stages of illness. This information would be needed to develop support services and to help target provision towards those most in need (Ashley et al. 2012). Furthermore, information on quality of life could guide clinical practice when used as a clinical predictor.
Despite these benefits, quality of life is still inadequately measured (Higginson 1999). Particularly disease-specific questionnaire for quality of life are needed as more generic questionnaires have been shown to not be relevant to all individuals with multiple myeloma and thus their use might compromise the scientific validity of clinical research (Osborne et al. 2012). With this questionnaire, inadequately managed symptoms and adverse psychosocial impact could be measured. There is also a need to understand experiences, symptoms and concerns of patients and their caregivers to adequately support them. The longitudinal nature of the study would allow to study complex trajectories and to study the interactions between problems over time. It might thus help predict how needs change over time in individuals with multiple myeloma, which would make it possible for care in the future to be targeted to those that need

Keeley 2008). Without this information, clinician will not be able to offer the best care available (Jubb 2002).

So far, the analysis has focused on the generic benefit that future individuals suffering from multiple myeloma might gain from this research. But there is also a substantial and growing body of research describing the specific benefits of participation for patients with life-limiting diseases and their families. These benefits can be therapeutic, cathartic, educational, empowering, altruistic and social in nature. The experiences of participants in such research have been the focus of two recent systematic reviews that suggest an overall benefit to participants (White & Hardy 2010, Gysels et al. 2012).
When focusing on studies involving surveys, interviews and observational or participatory methods positive effects are reported more commonly than negative effects to participants. In a study of 195 advanced cancers patients the majority of participants found a one hour-long interview a therapeutic experience (Barnett 2001). In a survey of 68 terminally ill cancer patients, 75% of participants reported no significant burden from taking part and 68% reported the encounter as beneficial because of the opportunity for social interaction and the opportunity to discuss their illness further (Pessin et al. 2008).

Participation in such research studies may often be therapeutic for some participants. In-depth qualitative interview studies of terminally ill participant's experiences of research have highlighted themes of benefit through social interaction and information provision (Gysels et al. 2008b) as well as enhanced problem solving skills, better coping mechanisms and feelings of empowerment, support and reassurance (Maloney et al. 2013). In a qualitative study of hospice patients, participants reflected that it was sometimes easier to discuss problems with researchers in more detail that might with their clinicians (Wright & Flemons 2002). Similarly, Eardley et al. (1991) found that research participants were able to discuss concerns that might not have arisen in a conversation with their doctor.

Altruism seems to be a particularly strong motive among those that participate in research. It was mentioned in almost all studies. Kendall and colleagues (2007) mention that research participants valued the opportunity to give something back and to help other people. They not only valued to provide information that benefitted others, they also used

research for sharing their experience about the care and services they had received in order to improve them (Kendall et al. 2007, Dobratz 2003). Similarly, family members or caregivers identified as important the knowledge that their involvement in research would assist future caregivers (Hudson 2003).

Patient participation may offer psychological benefits by conferring a sense of empowerment, autonomy or self-worth whilst living with a life-limiting disease. In a study of terminally ill home-hospice patients, participants discussed the valued opportunity to contribute to research that might help others despite their terminal illness (Dobratz 2003). Thus, participating in research can serve to empower participants for whom ill health resulted in a feeling of disempowerment and feeling undervalued, which can improve the quality of life, especially the role functioning, of participants (McGrath 2003, Hopkinson et al. 2005, Lee & Kristjanson 2003). Participants with advanced disease may feel that participation imparts a perceived sense of purpose and "usefulness" despite their diagnosis which may confer an extra psychological benefit (Terry et al. 2006). This finding was echoed in qualitative studies of hospice patient-participants (Ross & Cornbleet 2003, Terry et al. 2006). This ability to gain new insight or construct positive meaning from illness, together with a sense of satisfaction that participants might gain, can be viewed as a benefit.

Gysels et al. (2008) also found that a strong motive can be to contribute to research in order to raise greater awareness and knowledge about a rare disease. This finding already emerged from the cross-sectional study on quality of life in multiple myeloma which is currently published. Participants commented on the fact the myeloma is a rare cancer and that it is often not diagnosed in a timely fashion because general practitioners do not know enough about the disease. This became a motivation for these individuals to take part in research. Moreover, through participation in research, participants might gain extra information about their disease that might help them make sense of their experiences of symptoms, side-effects of treatment and problems and might help set these in a wider context (Eardley 1991). This increased knowledge about themselves and the opportunity for interaction with the researcher was also seen as a benefit in a longitudinal study of lung cancer patients by Murray & Sheikh (2006). Research by Gysels et al. (2008) has shown that one of the motives and benefits for participants might be to use research for seeking information or access to services or to use it as a sounding board for commenting on services. We will try help participants by providing them with information and access to information leaflets from Macmillan Cancer Support and Myeloma UK, if they wish to have this information. However, we will not be able to request specific changes to their treatment but will refer participants to their clinical team if these issues come up in the interviews.

Through self-monitoring of quality of life and symptoms patients might get extra benefit by getting better symptom management. This research might result in additional attention from health care practitioners because of routine monitoring of quality of life, for some at a time when they are seen infrequently in the outpatient haematology clinics and might result in picking up symptoms or problems that might need treatment earlier than usual (Arraf et al. 2004). This benefit was highlighted in six of 11 studies in a systematic review by Todd et al. (2009).

In summary, participants might experience benefit from taking part in this study by having the opportunity to help others through advancing the evidence base, by feeling empowered through role fulfilment and by getting information about their disease if they wish and by getting more attention and better symptom management from their clinical team. However, it must also be pointed out that not all participants will experience the same benefit. However, we aim at providing information to those who wish to have more, by giving patients the opportunity to talk about the spectrum of their experiences and by enhancing the evidence base, this research will result in benefit.

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A26. What are the potential risks for the researchers themselves? *(if any)*

A potential risk/harm for researchers can stem from witnessing suffering and from needing to engage in emotional labour as a consequence (Seymour & Ingleton 1999, Seymour et al. 2005, Clark et al. 2000). Also, some of the participants in the study might be asked to participate shortly after diagnosis, thus at a critical point in their life. Sensitive recruitment will be important in building relationships and establishing a long-term commitment to the study (Calman et al. 2013). Exploring sensitive emotional areas or dealing with distressed participants can lead to distress within the research team. Potential harm can also arise from the expectations that participants have of researchers, especially when they are expected to give help which they may not be able to give, or when they are perceived as a health care professionals (Evans et al. 2002). This role conflict can be distressing to the researcher, especially when he or she experiences guilt over not being able to appropriately help with serious and distressing symptoms that are experienced by the patients. This is especially true in longitudinal research, in which relationships to participants develop over time and problems with closure of relationships might arise (Calman et al. 2013). However, the emotional challenges of conducting longitudinal research with cancer patients have been found to be comparable to conducting research in other fields, such as long term disabilities (Kendall et al. 2007). A supportive network and close relationships to the clinical teams at the recruiting sites will be established to support the researchers in their role. If participants show signs of distress consent will be sought to contact their clinical team to address the symptom burden identified.

To address these problems, we have put a distress protocol in place. This entails that researchers screen returned questionnaires by patients for high symptoms and with consent of the patients inform the clinical team that looks after this patient about the high scores. We will also provide a training procedure to raise the awareness to some of the potential problems and to teach researchers the skills for managing difficult topics and emotions during the interview and how management might change as relationships deepen (Calman et al. 2013).

The leading researcher on this study has a degree in psychology and received training in counselling and communication skills. She is experienced in addressing emotional challenging situation with clients. In addition, supervision as needed will be provided by the academic supervisor. We will also develop a supportive network for researchers (i.e. debriefing sessions post-interviews, supervision), as suggested by Calman et al. (2013). The research will be conducted within the Department of Palliative Care, Policy and Rehabilitation a team with enormous experience conducting research in palliative and end of life care.

There will be regular meetings with the project steering group as well as informal peer support within the department. Access and support through supervision and supportive networks can address the risks for researchers that stem from witnessing suffering and from needing to engage in emotional labour (Seymour & Ingleton 1999, Seymour et al. 2005, Clark et al. 2000, Duke & Bennett 2010).

It is crucial for researchers to adhere to confidentiality and therefore to the guidelines for handling and storing data. In a longitudinal study with multiple data points, data is collected more than once on each participant. We will adhere strictly to principles of confidentiality, developing written procedures for managing contacts with participants and developing a plan for data transfer from paper forms to electronic files and data management. This is especially important because it fosters trust between researchers and participants (Calman et al. 2013).
Potential harm to the researcher and the staff being involved in providing the data can also arise from hidden costs in terms of time-consuming steps to be taken to approach potential participants, consent them into the study, help with data collection and attend briefing sessions and meetings regarding the research (Endacott 2007, Dobratz 2003). We address this issue by asking dedicated research staff in participating centres to screen and recruit potential participants. The principal investigators of the study sites are also part of the project steering group. The research nurses and the researcher in this project will assist the clinical staff in the participating centres whenever possible. Prior to setting up the study, the clinicians from the participating sites were involved in the development of the design, conduct and processes of research for this study (Duke & Bennett, 2010). We will follow guidance for supporting and communicating with staff recruiting research participants (Daniels & Exley 2001). We tried to reduce the burden of data collection for participating centres by minimising the role of the clinical members to screening and approaching participants only. All subsequent steps of the research process will be performed by the researchers of this study. Another potential problem associated with recruitment that can hinder the study's progress is gate-keeping. Gate-keeping has been highlighted as a problem in numerous reviews (Duke & Bennett 2010, Ewing et al. 2004, Kendall et al. 2007, Lee & Kristjanson 2003, Payne et al. 2007, White et al. 2008). To address this problem of accessing patients we will recruit at various centres and we will hold meetings and training sessions with the members of the clinical team at each site before recruitment starts. Staff at the participating centres have also taken part in the cross-sectional study on quality of life (REC ref: 10/H0808/133) and have successfully recruited patients for this study. We do not expect gate-keeping to be a significant problem in this longitudinal study.

We will offer participants to option of completing interviews or questionnaires at a time and place convenient to them. This may therefore require members of the research team to visit them in the community. This can pose potential harm for the researcher as home interviews have not the same degree of safeness as interviews in the hospital or research institutes facilities (Smith 1992). All those working offsite in this way are required to complete a log showing where they are going to conduct an interview. All researchers will be paired with a partner to ensure that a named individual within the department knows their whereabouts at all times.
However, in general the potential risks to the researchers themselves are considered to be minimal in this study, following experiences with longitudinal research in these groups and with longitudinal questionnaire-based research in general (Calman et al. 2013, Evans et al. 2002).

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RECRUITMENT AND INFORMED CONSENT

In this section we ask you to describe the recruitment procedures for the study. Please give separate details for different study groups where appropriate.

A27-1. How will potential participants, records or samples be identified? Who will carry this out and what resources will be used?*For example, identification may involve a disease register, computerised search of GP records, or review of medical records. Indicate whether this will be done by the direct healthcare team or by researchers acting under arrangements with the responsible care organisation(s).*

For all study phases, participants will be recruited from the haematology outpatient clinics or the inpatient units at the participating sites. In addition, patients with multiple myeloma under the care of the palliative home care team at St Christopher's Hospice will be recruited. All potential participants will be screened by a member of their clinical team familiar with the patient against the inclusion and exclusion criteria.

If screened as appropriate and eligible by the clinical team, potential participants will be given the Information Sheet by a clinician and have further discussion about the study with a member of the research team. This will offer them the opportunity to ask questions about the study. A member of the research team will take consent.

13 Appendix D: Patient information sheet, consent forms

Appendix D.1: Consent form, phase I 'Pilot survey'

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KING'S College LONDON

Participant Consent Form

Quality of Life of People with Myeloma – Pilot Survey

Study Identification Number:

		Circle as appropriate:
1.	I have read and understand the information sheet for the above study and have had the opportunity to ask questions.	Yes / No
2.	I understand that my participation is voluntary and that I am free to withdraw at any time, without giving a reason, and without my medical or legal rights being affected.	Yes / No
3.	I agree to be interviewed as I complete a questionnaire, and for this interview to be recorded electronically.	Yes / No
4.	I agree that relevant sections of my medical notes about the type of myeloma and the treatments I have received so far may be viewed by researchers from the Department of Palliative Care, Policy and Rehabilitation at King's College London, research nurses working on the study, or regulatory authorities from the NHS trust, where it is relevant to my taking part in this research.	Yes / No
5.	I agree that my details will be kept on an anonymised database, and that questionnaires and electronic recordings will be kept for a period of seven years.	Yes / No
6.	I agree that my anonymised views may be shared in scientific publications and at scientific meetings.	Yes / No

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7. I agree that the data collected may be used in an anonymised form for educational purposes in the future. Yes / No

8. I may be contacted by Professor Irene Higginson (the chief researcher) on the number below to check the standard of the interview and the conduct of junior researchers. Yes / No

_____

9. I agree for my GP to be informed about my participation in the study. Please give the name and contact details of your GP below: Yes / No

_____

_____

10. I would like to be informed about the results of the study. If you select 'Yes' you will be sent a summary by post - please be aware that it may take some years before the results are known. Please provide the address you wish it to be sent to: Yes / No

_____

_____

Participant:

Name:		Signature:		Date:	

Researcher:

Name:		Signature:		Date:	

----- Three copies of this form should be made for (1) participant, (2) researcher and (3) hospital/GP notes -------

Appendix D.2: Consent form, Phase II 'Patient Quality of Life Survey'

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KING'S College LONDON

Participant Consent Form

How Does Quality of Life of People with Myeloma Change Over Time – Patient Survey

Study Identification Number:

		Circle as appropriate:
1.	I have read and understand the information sheet for the above study and have had the opportunity to ask questions.	Yes / No
2.	I agree to take part in this study and I know that as a participant in this study I will be asked to fill out some questionnaires on five separate occasions in the next year.	Yes / No
3.	I understand that my participation is voluntary and that I am free to withdraw at any time during the study, without giving a reason, and without my medical or legal rights being affected.	Yes / No
4.	I agree that relevant sections of my medical notes about the type of myeloma and the treatments I have received so far may be viewed by researchers from the Department of Palliative Care, Policy and Rehabilitation at King's College London, research nurses working on the study, or regulatory authorities from the NHS trust, where it is relevant to my taking part in this research.	Yes / No
5.	I agree that my details will be kept on an anonymised database, and that questionnaires will be kept for a period of seven years.	Yes / No
6.	I agree that my anonymised responses may be shared in scientific publications and at scientific meetings.	Yes / No

7. I agree that the data collected may be used in an anonymised form for educational purposes in the future. Yes / No

8. I may be contacted by a member of the research team on the number below to check the standards and conduct of more junior researchers. Yes / No

_____

9. I agree for my GP to be informed about my participation in the study. Please give the name and contact details of your GP below: Yes / No

_____

_____

10. I would like to be informed about the results of the study. If you select 'Yes' you will be sent a summary by post - please be aware that it may take some years before the results are known. Please provide the address you wish it to be sent to: Yes / No

_____

_____

Participant:

Print Name:		Signature:		Date:	

Researcher:

Print Name:		Signature:		Date:	

------- *Three copies of this form should be made for (1) participant, (2) researcher and (3) participant's GP* -------

Appendix D.3: Consent form, phase II 'Caregiver Quality of Life Survey'

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Participant Consent Form

How Does Quality of Life of People with Myeloma Change Over Time – Carer Survey

Study Identification Number:

		Circle as appropriate:
1.	I have read and understand the information sheet for the above study and have had the opportunity to ask questions.	Yes / No
2.	I agree to take part in this study and I know that as a participant in this study I will be asked to fill out some questionnaires on three separate occasions in the next year.	Yes / No
3.	I understand that my participation is voluntary and that I am free to withdraw at any time during the study, without giving a reason, and without my medical or legal rights being affected.	Yes / No
4.	I agree that my details will be kept on an anonymised database, and that questionnaires will be kept for a period of seven years.	Yes / No
5.	I agree that my anonymised responses may be shared in scientific publications and at scientific meetings.	Yes / No
6.	I agree that the data collected may be used in an anonymised form for educational purposes in the future.	Yes / No
7.	I may be contacted by a member of the research team on the number below to check the standards and conduct of more junior researchers.	Yes / No

8. I agree for my GP to be informed about my participation in the study. Please give the name and contact details of your GP below: Yes / No

_____

_____

9. I would like to be informed about the results of the study. If you select 'Yes' you will be sent a summary by post - please be aware that it may take some years before the results are known. Please provide the address you wish it to be sent to: Yes / No

_____

_____

Participant:

Print Name:		Signature:		Date:	

Researcher:

Print Name:		Signature:		Date:	

------- *Three copies of this form should be made for (1) participant, (2) researcher and (3) participant's GP* -------

Appendix D.4: Information leaflet, phase I 'Pilot Quality of Life Survey'

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KING'S College LONDON

Study Information Sheet

Quality of Life of People with Myeloma – Pilot Survey

Investigators Christina Ramsenthaler, Research Assistant, King's College London.
Professor Irene Higginson, Professor of Palliative Care and Policy, King's College London.
Dr Steve Schey, Consultant Haematologist and Lead for Myeloma Services, King's College Hospital.
Dr Polly Edmonds, Consultant and Clinical Lead in Palliative Medicine, King's College Hospital.

You are being invited to take part in a study looking at the quality of life of people with myeloma.

Thank you for taking the time to read this leaflet. Before you decide if you would like to take part, we would like to tell you why the research is being done and what it would involve for you.
One of our team will go through this information sheet with you and answer any questions you may have. Please ask us if anything is not clear.

- *What is the purpose of the study?*

  We are trying to answer the question "What is the quality of life of people with myeloma?". We want to try and understand what it is like for people to live every day with myeloma. We want to know if certain groups of people have better or worse quality of life, and why that might be.

  We hope this will improve the care of people with myeloma in the future. With a better understanding of how the disease affects quality of life, we can try to focus our treatment to the things that matter most to patients.

- *Why have I been asked to take part?*

  Your medical team knows about this study. They have told us that you have myeloma and that you might be able to take part.

- *What will happen to me if I decide to take part?*

  Firstly thank you very much for your time. You will be asked to sign and date a consent form. A copy will be put in your medical notes and one copy kept by the research team.

  You will then be asked once to complete a questionnaire about various aspects of quality of life. As you complete the questionnaire we will ask you questions about it. You will be asked how difficult or easy you find it to answer the questions and what you think about the length of the questionnaire and about how the questionnaire is presented. Our discussion will be recorded and later analysed.

  We will ask you some details about you - including your age, ethnicity, religion, previous education and if you are currently employed.

  With your permission we will also get some details from your medical notes. A researcher or a research nurse working on the study will access the medical notes to get information on the type of myeloma you have, the date you were diagnosed and information on the treatments (e.g. the chemotherapeutic drugs) you have received so far. This information is needed to understand better which of these factors influence quality of life and wellbeing. All details will be kept anonymously.

- *How long will being in the study take?*

  It should take about 1 hour to complete. We will hold the interview at a place and time of your choice (for example your home or a private room in our research institute). If you want to have the interview at our research institute, the Cicely Saunders Institute, near King's College Hospital, we will be able to provide travel expenses.

- *Will my taking part be kept confidential?*

  All personal information collected about you will remain strictly confidential at all times. Any information we record about you will be anonymised so that you cannot be recognised from it.

- *Will my GP be told that I am part of the study?*

  Yes. We will normally let your GP know that you have taken part in this study, unless you would prefer us not to. Rarely, we might discover an urgent medical problem that is being poorly treated. If this happens, we might need to speak to your doctors, if you give us permission to do so.

- *What will happen to the results of the study?*

  We hope that the findings from the study will help improve the care of people with myeloma in the future. We hope that the results will be made available to other health care professionals by a series of articles published in scientific journals. No one person will be identifiable in any of these articles.

- *What are the disadvantages or risks of taking part?*

  Some people might find questions about their health and well-being upsetting. Firstly, we are sorry if this happens and we will help where we can. You may miss out any questions you find upsetting or come back to them later, if you want to. You can decide to stop being in the study at any time.

  The questionnaire asks about symptoms and problems you might or might not experience (e.g. having pain, being short of breath, feeling anxious). If the questions show that a symptom or issue is particularly severe, we would ask you if you wanted this to be addressed. If yes, we would with your permission contact your doctor, nurse or GP or we could put you in touch with the Myeloma UK Infoline.

- *What are potential benefits of taking part?*

  We cannot promise that they study will help you. The information we get from this study will help to improve the assessment of people with myeloma.
  In similar studies, people value the opportunity to explain about any problems and symptoms they might have and how this has affected their wellbeing and quality of life.

- *Who is organising and funding the study?*

  This study is supported by grants from Myeloma UK and St Christopher's Hospice. This research has been reviewed by the Central London Regional Ethics Committee.

- *Do I have to take part?*

  No. It is entirely up to you to decide whether or not to take part in the study. If you decide to take part you can withdraw at any time and without giving a reason.

- *What will happen if I decide not to take part?*

  If you decide not to take part *it will not affect your medical care in any way.*

  We respect your decision not to take part, but it would be very helpful for us to know a bit more about you, and why you have said no. We will therefore ask you why, and for

your permission to retrieve some anonymous details from your medical notes. This is because we want to make sure the final group of study participants is typical of the whole range of people with myeloma.

However, you do not have to give a reason for saying no, and you don't have to give permission for use to take details from your notes. We will respect your wishes.

- *If I have more questions, who can I ask?*

  Please feel free to ask me any questions about the study.

Thank you very much for taking the time to find out about our study. Please feel free to contact me if you have any questions or concerns. My contact details are:

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Appendix D.5: Information leaflet, phase II 'Patient Quality of Life Survey'

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KING'S College LONDON

Study Information Sheet

How Does Quality of Life of People with Myeloma Change Over Time – Patient Survey

Investigators Christina Ramsenthaler, Research Assistant, King's College London.
Professor Irene Higginson, Professor of Palliative Care and Policy, King's College London.
Dr Steve Schey, Consultant Haematologist and Lead for Myeloma Services, King's College Hospital.
Dr Polly Edmonds, Consultant and Clinical Lead in Palliative Medicine, King's College Hospital.

You are being invited to take part in a study looking at the quality of life of people with myeloma.

Thank you for taking the time to read this leaflet. Before you decide if you would like to take part, we would like to tell you why the research is being done and what it would involve for you.
One of our team will go through this information sheet with you and answer any questions you may have. Please ask us if anything is not clear.

- *What is the purpose of the study?*

  We are trying to answer the question "What is the quality of life of people with myeloma and how does quality of life change over time?". We want to try and understand what it is like for people to live every day with myeloma. We want to know if certain groups of people have better or worse quality of life, and why that might be. We also want to know what affects quality of life of myeloma patients over time throughout the disease.

  We hope this will improve the care of people with myeloma in the future. With a better understanding of how the disease affects quality of life, we can try to focus our assessment to the things that matter most to patients.

- *Why have I been asked to take part?*

  Your medical team knows about this study. They have told us that you have myeloma and that you might be able to take part.

- *What will happen to me if I decide to take part?*

  We would like to ask you, and the person who helps care for you, to fill in questionnaires about various aspects of quality of life. These questionnaires contain questions about how your illness affects your life, what symptoms may trouble you and what care you have received in the past.

  This study does not include any new medicine or treatments.

  If you decide to take part, you will be asked to sign and date a consent form. A copy will be put in your medical notes and one copy will be kept by the research team.

  The research team will contact you up to five times during the year and ask you to fill in a questionnaire booklet on each occasion. This can be done at home. You will be contacted every two months over the period of one year. Overall this means filling in questionnaires on five occasions. Filling in the questionnaire can take 40-90 minutes each time. The questionnaire will be slightly different each time you fill it out. It will contain questions on:
  - the symptoms or problems you might or might not experience
  - how well you feel emotionally and what you might worry about
  - how much you are able to do what you want to do and how myeloma is affecting this
  - the health care services (e.g. drugs, hospital visits) you have received.

  We will send the questionnaire to your home and give you a Freepost envelope to send it back to us once you have filled it out. If you have questions about the questionnaire or would like to fill it in with the help of another person, we can call you and help you with filling it in over the phone. If we have not received the questionnaire back within 3-4 weeks of posting it to you, we may contact you by phone to ask how you are getting on and see if there is any help we can give you to complete it.

  With your permission, we might also telephone you if, when we have received the questionnaire we have any questions about your answers.

  Your main carer (if you have one) would also be approached to ask them if they would be willing to complete another questionnaire. This questionnaire asks them about their health and what kinds of help you need with living with your illness. They do not need to be asked by us to take part in the study if you wish so. You can take part in this study regardless whether your main carer wants to take part or not.

  We will also ask you some details about you at the beginning of the study - including your age, ethnicity, religion, previous education and if you are currently employed.

With your permission we will also get some details from your medical notes. A researcher or a research nurse working on the study will access the medical notes to get information on the type of myeloma you have, the date you were diagnosed and information on the treatments (e.g. the chemotherapeutic drugs) you have received so far. This information is needed to understand better which of these factors influence quality of life and wellbeing. All details will be kept anonymously.

- *Will my taking part be kept confidential?*

  All personal information collected about you will remain strictly confidential at all times. Any information we record about you will be anonymised so that you cannot be recognised from it.

- *Will my GP be told that I am part of the study?*

  Yes. We will normally let your GP know that you have taken part in this study, unless you would prefer us not to. Rarely, we might discover an urgent medical problem that is being poorly treated. If this happens, we might need to speak to your doctors, if you give us permission to do so.

- *What will happen to the results of the study?*

  We hope that the findings from the study will help improve the care of people with myeloma and those that help care for them in the future. We hope that the results will be made available to other health care professionals by a series of articles published in scientific journals. No one person will be identifiable in any of these articles.

- *What are the disadvantages or risks of taking part?*

  Some people might find questions about their health and well-being upsetting. Firstly, we are sorry if this happens and we will help where we can. You may miss out any questions you find upsetting or come back to them later, if you want to. You can decide to stop being in the study at any time.

  The questionnaire asks about symptoms and problems you might or might not experience (e.g. having pain, being short of breath, feeling anxious). If the questions show that a symptom or issue is particularly severe, we would ask you if you wanted this to be addressed. If yes, we would with your permission contact your doctor, nurse or GP or we could put you in touch with the Myeloma UK Infoline.

- *What are potential benefits of taking part?*

  We cannot promise that the study will help you. The information we get from this study will help to improve the assessment of people with myeloma.

  In similar studies, people value the opportunity to explain about any problems and symptoms they might have and how this has affected their wellbeing and quality of life.

We would like to call you around the time of the questionnaire being mailed to you. This will allow you to tell us about any questions or concerns you might have about the questionnaire. You will also be offered information leaflets from Myeloma UK and Macmillan Cancer Support, if you wish.

- *Who is organising and funding the study?*

  This study is supported by grants from Myeloma UK and St Christopher's Hospice. This research has been reviewed by the Central London Regional Ethics Committee.

- *Do I have to take part?*

  No. It is entirely up to you to decide whether or not to take part in the study. If you decide to take part, you can withdraw at any time and without giving a reason.

- *What will happen if I decide not to take part?*

  If you decide not to take part *it will not affect your medical care in any way.*

  We respect your decision not to take part, but it would be very helpful for us to know a bit more about you, and why you have said no. We will therefore ask you why, and for your permission to retrieve some anonymous details from your medical notes. This is because we want to make sure the final group of study participants is typical of the whole range of people with myeloma.

  However, you do not have to give a reason for saying no, and you don't have to give permission for use to take details from your notes. We will respect your wishes.

- *If I have more questions, who can I ask?*

  Please feel free to ask me any questions about the study.

Thank you very much for taking the time to find out about our study. Please feel free to contact me if you have any questions or concerns. My contact details are:

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Appendix D.6: Information leaflet, phase II 'Caregiver Quality of Life Survey'

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KING'S College LONDON

Study Information Sheet

How Does Quality of Life of People with Myeloma Change Over Time – Carer Survey

Investigators Christina Ramsenthaler, Research Assistant, King's College London.
Professor Irene Higginson, Professor of Palliative Care and Policy, King's College London.
Dr Steve Schey, Consultant Haematologist and Lead for Myeloma Services, King's College Hospital.
Dr Polly Edmonds, Consultant and Clinical Lead in Palliative Medicine, King's College Hospital.

You are being invited to take part in a study looking at the quality of life of people with myeloma.

Thank you for taking the time to read this leaflet. Before you decide if you would like to take part, we would like to tell you why the research is being done and what it would involve for you.
One of our team will go through this information sheet with you and answer any questions you may have. Please ask us if anything is not clear.

- *What is the purpose of the study?*

  We are trying to answer the question "What is the quality of life of people with myeloma and how does quality of life change over time?". We want to try and understand what it is like for people to live every day with multiple myeloma. We want to know if certain groups of people have better or worse quality of life, and why that might be. We also want to explore what it is like for family and friends who help people with myeloma. We would like to understand what worries and concerns your family member's or friend's illness gives you.

  We will use this information to make care better for patients with myeloma and the family members and friends caring for them.

- *Why have I been asked to take part?*

  Your family member or friend who has myeloma has been asked to take part in our study. They have told us you help care for them at home and might be able to take part.

- *Do I have to take part?*

  No. It is entirely up to you to decide whether or not to take part in the study. If you decide to take part you can withdraw at any time and without giving a reason. If you decide not to take part this will NOT affect any aspect of the care or treatment that you, your family member or friend receive.

- *What will happen to me if I decide to take part?*

  If you decide to take part, the study will be explained to you in more detail. You will be asked to sign and date a consent form. A copy will be put in your medical notes and one copy will be kept by the research team.

  Your family member or friend has been asked to take part in a study asking them about their experiences of living with myeloma and how this affects their quality of life. We want to ask you as a family member or friend of a person living with myeloma what your experiences or concerns are regarding their health, what help you offer them and what difficulties you experience. We will ask about your own health and about symptoms you may or may not have. There are also questions about your family member's or friend's health.

  The research team will contact you up to three times during the year and ask you to fill in a questionnaire booklet on each occasion. This can be done at home. You will be contacted every four months over the period of one year. Overall this means filling in the questionnaire on three occasions. Filling in the questionnaire takes about 40-90 minutes each time. The questionnaire will be slightly different each time you fill it out. It will contain questions on:
  - your experiences of caring for a family member or friend with myeloma
  - the problems you might experience
  - your health and wellbeing
  - your family member's or friend's health and wellbeing.

  We will send the questionnaire to your home and give you a Freepost envelope to send it back to us once you have filled it in. If you have questions about the questionnaire or would like to fill it in with the help of another person, we can call you and help you filling it out over the phone. If we have not received the questionnaire back within 3-4 weeks of posting it to you, we may contact you by phone to ask how you are getting on and see if there is any help we can give you to complete it.

With your permission, we might also telephone you if, when we have received the questionnaire we have any questions about your answers.

We will also ask you some details about you at the beginning of the study - including your age, ethnicity, religion, previous education and if you are currently employed. All details will be kept anonymously.

This study does not include any new medicine or treatments.

- *Will my taking part be kept confidential?*

  All personal information collected about you will remain strictly confidential at all times. Any information we record about you will be anonymised so that you cannot be recognised from it.

- *Will my GP be told that I am part of the study?*

  Yes. We will normally let your GP know that you have taken part in this study, unless you would prefer us not to. Rarely, we might discover an urgent medical problem that is being poorly treated. If this happens, we might need to speak to your doctors, if you give us permission to do so.

- *What will happen to the results of the study?*

  We hope that the findings from the study will help improve the care of people with myeloma and those that help care for them in the future. We hope that the results will be made available to other health care professionals by a series of articles published in scientific journals. No one person will be identifiable in any of these articles.

- *What are the disadvantages or risks of taking part?*

  Some people might find questions about their health and well-being upsetting. Firstly, we are sorry if this happens and we will help where we can. You may miss out any questions you find upsetting or come back to them later, if you want to. You can decide to stop being in the study at any time.

  The questionnaire asks about symptoms and problems you might or might not experience (e.g. having pain, being short of breath, feeling anxious). If the questions show that a symptom or issue is particularly severe, we would ask you if you wanted this to be addressed. If yes, we would with your permission contact your doctor, nurse or GP or we could put you in touch with the Helpline from Carers UK.

- *What are potential benefits of taking part?*

  We cannot promise that the study will help you or your friend or family member. The information we get from this study will help to improve the future assessment and care of people with myeloma.

In similar studies, most people value the opportunity to explain about any problems and symptoms they might have and how this has affected their well-being and their family member's or friend's well-being. We would like to call you around the time of the questionnaire being mailed to you. This will allow you to tell us about any questions or concerns you might have about the questionnaire. You will also be offered information leaflets from Myeloma UK and Macmillan Cancer Support, if you wish.

- *Who is organising and funding the study?*

  This study is supported by grants from Myeloma UK and St Christopher's Hospice. This research has been reviewed by the Central London Regional Ethics Committee.

- *What will happen if I decide not to take part?*

  If you decide not to take part *it will not affect your medical care in any way.*

  We respect your decision not to take part, but it would be very helpful for us to know a bit more about you, and why you have said no. We will therefore ask you why, and for your permission to retrieve some anonymous details from your medical notes. This is because we want to make sure the final group of study participants is typical of the whole range of people with myeloma.

  However, you do not have to give a reason for saying no, and you don't have to give permission for use to take details from your notes. We will respect your wishes.

- *If I have more questions, who can I ask?*

  Please feel free to ask me any questions about the study.

Thank you very much for taking the time to find out about our study. Please feel free to contact me if you have any questions or concerns. My contact details are:

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Denmark Hill
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14 Appendix E: Topic guide for piloting

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KING'S College LONDON

Interview schedule

Longitudinal quality of life in multiple myeloma – Pilot Interviews (Phase I)

Objective:

- To establish best methods for a longitudinal survey of quality of life in patients with multiple myeloma and their informal caregivers and to explore their experiences, preferences and expectations.
- Method: Face-to-face interviews

- *Introduction:*
  - Introduction of researcher
  - Purpose of interview: Thank you very much for seeing me for this interview. We would like your comments about a study we are planning. We want to make sure that we conduct the study in the best possible way and make sure the information we provide and other documents we use are right.
  - Content of interview: The study we are planning will involve interviews with patients and their nearest family member or friend that helps care for them. We would like to hear your views on the best way we can carry out the interviews. The interview will be about quality of life, how it may have changed since being diagnosed with multiple myeloma, about symptoms and problems experienced and services used. We plan to ask a questionnaire to ask about these issues.
  - Confidentiality: Any comments you make will be confidential to the study and will not affect the care you receive (unless there is any information that you would prefer your doctor or nurse to know). Please do not use names of doctors and nurses.
    - The interview should not last longer than one hour.
    - If you want to stop at any time please feel free to say so.
    - I would like to tape-record the interview to make sure that I understand, accurately, everything you say. Once transcribed the tape will be destroyed and no names will be attached to any information we receive. You can also ask me to turn off the tape if you want to mention something that you don't want to be taped.
    - There are no right or wrong answers. Please tell us what you think. If you don't want to answer a question that is fine.
    - Do you have any questions?
- *Sign consent forms*
  - I'll start the recording now if that's alright with you.

---------- START RECORDING ----------

A. Preferences for study procedures – approach to study

Thinking about *taking part in an interview*

1. Have you been interviewed as part of a study before Yes □ No □
2. If yes, did you enjoy the interview Yes □ No □

Can you say a little more about why

3. What did you think about being interviewed today?
4. Were you worried in any way about what our questions might be?

Can you tell me a little more about this?

5. Is there any way that we can reassure people about the content of this study?
6. Would any more information have made you more confident about the interview today?

Can you give me some examples?

B. Questionnaires

We will be using the following questionnaire to get people's views on how having multiple myeloma affects them and their quality of life, some of their problems and concerns and the services they use. Please take a few minutes to look through (hand them draft questionnaire).

1. ***Clear*: Do the questions seem clear to you** Yes □ No □
2. ***Information***: Is there enough information to help you answer the questions? Yes □ No □
3. ***Not answer***: Are there any questions that you would not want to answer? Yes □ No □
4. ***Priorities***: - Any issues in the questionnaire particularly important or relevant to your QOL?
   - Any issues in the questionnaire that are not / are less important your QOL?
5. ***Gaps:*** - Are there any issues important to you that are not included in the questionnaires?

   Probe: Thinking about your life at the moment – what things are most important to your quality of life?
6. **Would you say the questionnaire looks:**

   A bit short □ About the right length □ A bit long □ Much too long □ Don't know □

   If too long – what part could we take out?
7. **Would you prefer**

   (a) to complete the questionnaire yourself (ticking a box or writing out your response) □

   (b) an interviewer asking questions and writing down your answers □

   (c) no preference □

   Can you tell me little more about your preferences?
8. **Where would you prefer to be interviewed?**

   (a) at home □

   (b) at the hospital □

   (c) another place, please say where..... □

9. **Would you prefer**

   (a) an interview face-to-face □

   (b) An interview over the phone □

   (c) A questionnaire to be sent to you at home, for you to complete and send back □

   (d) No preference

   What are your thoughts on these types of interview/questionnaire completion?

10. **What would be the best time for you for an interview? About what time?**

    (a) Morning

    (b) Afternoon

    (c) Evening

    (d) No preference

    Is there any particular reason for this? Probe on at least favourite time?

C. Preferences for study procedures – staying in touch and follow-up

Now, thinking about how I made contact with you

1. **What were your first thoughts when you were told about the study?**
2. **You were given an information sheet. Did it give you enough information about our study?**

   Yes □ No □

   - can you remember anything in particular about it

   - What did you think about it

   - What did you like and dislike

   - Was there anything else you would like to know more about?

   - Was the information sheet easy to read?

   - Do you have any suggestions about how we could improve it?

3. **Thinking about making contact with you again: We want to know more about what patients think of their illness and care received over time. Would you be willing to take part in more interviews?**

   Yes □ No □

4. **If yes, what do you think would be the best period of time to contact you again?**

   In how many weeks/months?

   Can you say a little more about why you think that is best?

   Would the be the best time period for regular interviews over time?

5. **What do you think is the best way to contact you or someone else about taking part in our study?**

   Telephone □

   Letter □

   No preference □

   Can you say a little more about why do you think that is best?

D. Preferences for study procedures – carer survey

1. **We are interested in talking to family members or friends who may provide some help, care or support for people to find out their views about the help you are getting.**
2. **Can you tell me if there are any family members or friends who help or support you?**

   Yes □ No □

   How often do you see them?

   In what ways do they help you?
3. **If yes, we would very much like to talk to the main person that helps or cares for people taking part in the study. Do you think this would be alright in general?**

   Yes □ No □
4. **Would it be agreeable to contact them by telephone?** Yes □ No □
5. **When would be the best time of day to contact them?**

   Morning □

   Afternoon □

   Evening □

E. Quality of life

1. **Has your quality of life changed in your life lately?**
   a. Did you experience any negative changes in your quality of life lately?
   b. Did you experience any positive changes in your quality of life lately? Has anything been particularly good or bad for you in the last month?
   c. Do you feel that there are any ways in which health professionals could have helped to make the last few months easier for you?
   d. How often has your quality of life changed in the past (around which events)?
2. **Is there anything else you might like to add?**

---------- THANKS + STOP RECORDING ----------

---------- COMPLETION OF DEMOGRAPHICS FORM ----------

15 Appendix F: Questionnaire booklets

Appendix F.1: Example questionnaire booklet from the Patient QOL Survey

KING'S College LONDON

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King's College Hospital NHS
NHS Foundation Trust

Professor Irene Higginson BMedSci BMBS FFPHM PhD FRCP, Head of Department
Professor Lynne Turner-Stokes DM FRCP, Herbert Dunhill Chair of Rehabilitation

How does quality of life of people with myeloma change over time?

Questionnaire Booklet for People with Multiple Myeloma

Study Identification Number: _____

Date Questionnaire Completed: _____

Setting Questionnaire Completed: (please tick)

- Hospital Outpatient: ❑
- Hospital Inpatient: ❑
- Home: ❑
- Other: _____

- *This is the fourth questionnaire of five. Again, this is a research questionnaire and we will ask about some issues more than once, but in a slightly different way.*
- *Please answer all the questions if possible. If you cannot remember, do not know the answer, or are unable to answer a particular question, please write that in.*
- *The final page of this booklet is left blank for you to write down any other comments you might have about the questionnaire.*

Thank you very much. Please feel free to contact me if you have any questions or concerns:

Christina Ramsenthaler ***christina.ramsenthaler@kcl.ac.uk*** ***Tel: 0207 848 5636***

~ Part A : Your problems and concerns ~

Please answer the following questions by ticking the box that is most true for you. It is important to answer all of the questions if possible. Your answers will be used to help improve your care and the care of others.

Thank you.

A1) What are your main problems or concerns at the moment?

1. _____
2. _____
3. _____

A2) Below is a list of symptoms, which you may or may not have experienced. For each symptom please tick one box that best describes how it has affected you over the past week.

	No, not at all	*Slightly*	*Moderately*	*Severely*	*Overwhelmingly*
Pain	0 ❑	1 ❑	2 ❑	3 ❑	4 ❑
Shortness of breath	0 ❑	1 ❑	2 ❑	3 ❑	4 ❑
Weakness or lack of energy	0 ❑	1 ❑	2 ❑	3 ❑	4 ❑
Nausea (feeling like you are going to be sick)	0 ❑	1 ❑	2 ❑	3 ❑	4 ❑
Vomiting (being sick)	0 ❑	1 ❑	2 ❑	3 ❑	4 ❑
Poor appetite	0 ❑	1 ❑	2 ❑	3 ❑	4 ❑
Constipation	0 ❑	1 ❑	2 ❑	3 ❑	4 ❑
Sore or dry mouth	0 ❑	1 ❑	2 ❑	3 ❑	4 ❑
Drowsiness	0 ❑	1 ❑	2 ❑	3 ❑	4 ❑
Poor mobility	0 ❑	1 ❑	2 ❑	3 ❑	4 ❑
Diarrhoea	0 ❑	1 ❑	2 ❑	3 ❑	4 ❑
Tingling in the hands and / or feet	0 ❑	1 ❑	2 ❑	3 ❑	4 ❑
Difficulty remembering things	0 ❑	1 ❑	2 ❑	3 ❑	4 ❑

Please list any other symptoms not mentioned above, and tick one box to show how they have affected you over the past week.

1.	0 ❑	1 ❑	2 ❑	3 ❑	4 ❑
2.	0 ❑	1 ❑	2 ❑	3 ❑	4 ❑
3.	0 ❑	1 ❑	2 ❑	3 ❑	4 ❑

		No, not at all	*Occasionally*	*Sometimes*	*Most of the time*	*Yes, always*
A3)	**Over the past week, have you been feeling anxious or worried about your illness or treatment?**	0 ❑	1 ❑	2 ❑	3 ❑	4 ❑
A4)	**Over the past week, have any of your family or friends been anxious or worried about you?**	0 ❑	1 ❑	2 ❑	3 ❑	4 ❑
A5)	**Over the past week, have you been feeling depressed?**	0 ❑	1 ❑	2 ❑	3 ❑	4 ❑

		Yes, always	*Most of the time*	*Sometimes*	*Occasionally*	*No, not at all*
A6)	**Over the past week, have you felt at peace?**	0 ❑	1 ❑	2 ❑	3 ❑	4 ❑

		Yes, as much as I wanted	*Most of the time*	*Sometimes*	*Occasionally*	*No, not at all*
A7)	**Over the past week, have you been able to share how you are feeling with your family or friends?**	0 ❑	1 ❑	2 ❑	3 ❑	4 ❑

		Enough information *the right amount for me*	*Information received* *but hard to understand*	*Information received* *but would like more*	*Very little information* *and would like more*	*No information received* *and would like information*
A8)	**Over the past week, have you had as much information as you wanted?**	0 ❑	1 ❑	2 ❑	3 ❑	4 ❑

		No problems/ Problems addressed	*Problems being addressed*	*Problems partly addressed*	*Most problems not addressed*	*Problems not addressed at all*
A9)	**Over the past week, have any practical matters resulting from your illness been addressed? (such as financial or personal)**	0 ❑	1 ❑	2 ❑	3 ❑	4 ❑

	Yes, as much as I wanted	*Most of the time*	*Sometimes*	*Occasionally*	*No, not at all*
A10) Over the past week, have you been able to carry out your usual activities without help from others?	0 ❑	1 ❑	2 ❑	3 ❑	4 ❑
A11) Over the past week, have you been able to pursue your hobbies and leisure activities?	0 ❑	1 ❑	2 ❑	3 ❑	4 ❑
A12) Over the past week, have you been able to spend quality time with family and friends?	0 ❑	1 ❑	2 ❑	3 ❑	4 ❑

We would like you to answer this question whether or not you are sexually active

Or if you would prefer not to answer then please tick here: ❑

	No, not at all	*Occasionally*	*Sometimes*	*Most of the time*	*Yes, always*
A13) Over the past week, have you been worrying about your sex life?	0 ❑	1 ❑	2 ❑	3 ❑	4 ❑

	No, not at all	*Occasionally*	*Sometimes*	*Most of the time*	*Yes, always*
A14) Over the past week, have you been worrying about infections?	0 ❑	1 ❑	2 ❑	3 ❑	4 ❑
A15) Over the past week, have you been worrying about your physical appearance?	0 ❑	1 ❑	2 ❑	3 ❑	4 ❑
A16) Over the past week, have you been worrying about your financial situation?	0 ❑	1 ❑	2 ❑	3 ❑	4 ❑
A17) Over the past week, have you been worrying that your illness will get worse?	0 ❑	1 ❑	2 ❑	3 ❑	4 ❑

	Yes, always	*Most of the time*	*Sometimes*	*Occasionally*	*No, not at all*
A18) Over the past week, have you felt able to cope with your illness and treatment?	0 ❑	1 ❑	2 ❑	3 ❑	4 ❑
A19) Are you able to contact your doctors or nurses for advice if needed?	0 ❑	1 ❑	2 ❑	3 ❑	4 ❑
A20) Do your doctors and nurses show a good standard of knowledge and skill when treating you?	0 ❑	1 ❑	2 ❑	3 ❑	4 ❑
A21) Do your doctors and nurses show care and respect when treating you?	0 ❑	1 ❑	2 ❑	3 ❑	4 ❑

	Enough information the right amount for me	*Information received but hard to understand*	*Information received but would like more*	*Very little information and would like more*	*No information received and would like information*
A22) Do you have enough information about what might happen to you in the future?	0 ❑	1 ❑	2 ❑	3 ❑	4 ❑

	On my own	*With help from a friend or relative*	*With help from a staff member*
A23) How did you complete this questionnaire?	0 ❑	1 ❑	2 ❑

Thank you for your time If you are worried about any of the issues raised on this questionnaire then please speak to your doctor or nurse.

~ Part B: Your physical wellbeing and symptoms ~

We are interested in some things about you and your health. Please answer all of the questions yourself by ticking the box that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

	Not at All	A Little	Quite a Bit	Very Much
B1) Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1 ❑	2 ❑	3 ❑	4 ❑
B2) Do you have any trouble taking a long walk?	1 ❑	2 ❑	3 ❑	4 ❑
B3) Do you have any trouble taking a short walk outside of the house?	1 ❑	2 ❑	3 ❑	4 ❑
B4) Do you need to stay in bed or a chair during the day?	1 ❑	2 ❑	3 ❑	4 ❑
B5) Do you need help with eating, dressing, washing yourself or using the toilet?	1 ❑	2 ❑	3 ❑	4 ❑

During the past week:

	Not at All	A Little	Quite a Bit	Very Much
B6) Were you limited in doing either your work or other daily activities?	1 ❑	2 ❑	3 ❑	4 ❑
B7) Were you limited in pursuing your hobbies or other leisure time activities?	1 ❑	2 ❑	3 ❑	4 ❑
B8) Were you short of breath?	1 ❑	2 ❑	3 ❑	4 ❑
B9) Have you had pain?	1 ❑	2 ❑	3 ❑	4 ❑
B10) Did you need to rest?	1 ❑	2 ❑	3 ❑	4 ❑
B11) Have you had trouble sleeping?	1 ❑	2 ❑	3 ❑	4 ❑
B12) Have you felt weak?	1 ❑	2 ❑	3 ❑	4 ❑
B13) Have you lacked appetite?	1 ❑	2 ❑	3 ❑	4 ❑
B14) Have you felt nauseated?	1 ❑	2 ❑	3 ❑	4 ❑
B15) Have you vomited?	1 ❑	2 ❑	3 ❑	4 ❑
B16) Have you been constipated?	1 ❑	2 ❑	3 ❑	4 ❑
B17) Have you had diarrhoea?	1 ❑	2 ❑	3 ❑	4 ❑
B18) Were you tired?	1 ❑	2 ❑	3 ❑	4 ❑
B19) Did pain interfere with your daily activities?	1 ❑	2 ❑	3 ❑	4 ❑

During the past week:

	Not at All	A Little	Quite a Bit	Very Much
B20) Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1 ❑	2 ❑	3 ❑	4 ❑
B21) Did you feel tense?	1 ❑	2 ❑	3 ❑	4 ❑
B22) Did you worry?	1 ❑	2 ❑	3 ❑	4 ❑
B23) Did you feel irritable?	1 ❑	2 ❑	3 ❑	4 ❑
B24) Did you feel depressed?	1 ❑	2 ❑	3 ❑	4 ❑
B25) Have you had difficulty remembering things?	1 ❑	2 ❑	3 ❑	4 ❑
B26) Has your physical condition or medical treatment interfered with your family life?	1 ❑	2 ❑	3 ❑	4 ❑
B27) Has your physical condition or medical treatment interfered with your social activities?	1 ❑	2 ❑	3 ❑	4 ❑
B28) Has your physical condition or medical treatment caused you financial difficulties?	1 ❑	2 ❑	3 ❑	4 ❑

For the following questions please circle the number between 1 and 7 that best applies to you

B29) How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

B30) How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Please indicate the extent to which you have experienced the following symptoms or problems during the past week. Please answer by ticking the box that best applies to you.

During the past week:	*Not at All*	*A Little*	*Quite a Bit*	*Very Much*
B31) Have you had bone aches or pain?	1 ❑	2 ❑	3 ❑	4 ❑
B32) Have you had pain in your back?	1 ❑	2 ❑	3 ❑	4 ❑
B33) Have you had pain in your hip?	1 ❑	2 ❑	3 ❑	4 ❑
B34) Have you had pain in your arm or shoulder?	1 ❑	2 ❑	3 ❑	4 ❑
B35) Have you had pain in your chest?	1 ❑	2 ❑	3 ❑	4 ❑
B36) If you had pain did it increase with activity?	1 ❑	2 ❑	3 ❑	4 ❑
B37) Did you feel drowsy?	1 ❑	2 ❑	3 ❑	4 ❑
B38) Did you feel thirsty?	1 ❑	2 ❑	3 ❑	4 ❑
B39) Have you felt ill?	1 ❑	2 ❑	3 ❑	4 ❑
B40) Have you had a dry mouth?	1 ❑	2 ❑	3 ❑	4 ❑
B41) Have you lost any hair?	1 ❑	2 ❑	3 ❑	4 ❑
B42) Answer this question only if you lost any hair: Were you upset by the loss of your hair?	1 ❑	2 ❑	3 ❑	4 ❑
B43) Did you have tingling hands or feet?	1 ❑	2 ❑	3 ❑	4 ❑
B44) Did you feel restless or agitated?	1 ❑	2 ❑	3 ❑	4 ❑
B45) Have you had acid indigestion or heartburn?	1 ❑	2 ❑	3 ❑	4 ❑
B46) Have you had burning or sore eyes?	1 ❑	2 ❑	3 ❑	4 ❑
B47) Have you felt physically less attractive as a result of your disease or treatment?	1 ❑	2 ❑	3 ❑	4 ❑
B48) Have you been thinking about your illness?	1 ❑	2 ❑	3 ❑	4 ❑
B49) Have you been worried about dying?	1 ❑	2 ❑	3 ❑	4 ❑
B50) Have you worried about your health in the future?	1 ❑	2 ❑	3 ❑	4 ❑

~ Part C : Your general health ~

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

C1) **Mobility**

I have no problems in walking about	❑
I have some problems in walking about	❑
I am confined to bed	❑

C2) **Self-Care**

I have no problems with self-care	❑
I have some problems washing or dressing myself	❑
I am unable to wash or dress myself	❑

C3) **Usual Activities** *(e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities	❑
I have some problems with performing my usual activities	❑
I am unable to perform my usual activities	❑

C4) **Pain/Discomfort**

I have no pain or discomfort	❑
I have moderate pain or discomfort	❑
I have extreme pain or discomfort	❑

C5) **Anxiety/Depression**

I am not anxious or depressed	❑
I am moderately anxious or depressed	❑
I am extremely anxious or depressed	❑

~ Part D : The healthcare you have received ~

We would like to know about the care you have received over the last 4 months. This includes health and social services (NHS or private) and also any help from family members or friends.

1. Did you stay overnight in…	Yes ▼	No ▼	How many days? (*please write down*) ▼
A hospital <u>intensive care</u> unit?	☐1	☐2	☐ days
Another hospital unit or ward?	☐1	☐2	☐ days
A nursing home?	☐1	☐2	☐ days
A residential home?	☐1	☐2	☐ days
A hospice?	☐1	☐2	☐ days

2. Did you visit...	Yes ▼	No ▼	How many times? (*please write down*) ▼
An Accident & Emergency (A&E) department?	☐1	☐2	☐ times
Did you use ambulance services?	☐1	☐2	☐ times
An outpatient haematology clinic?	☐1	☐2	☐ times
An outpatient clinic for chemotherapy?	☐1	☐2	☐ times
An outpatient clinic for radiotherapy?	☐1	☐2	☐ times
An outpatient clinic for other appointments? (for example, blood transfusions, scans, treatments etc.)	☐1	☐2	☐ times
A day care centre? (for example, a day care centre in a hospice)	☐1	☐2	☐ times

3. Please give details of any services you used while you were not in hospital during the past 4 months. Please include face-to-face and telephone contacts.

Did you have contact with...	Yes ▼	No ▼	How many times? (*please write down*) ▼
GPs or family doctors – face-to-face? ……..... (for example, at home, in the GP practice, nursing home)	☐1	☐2	☐ times
GPs or family doctors – on the telephone? ……..... (for example for prescriptions, test results etc.)	☐1	☐2	☐ times
A district nurse or community nurse?.....	☐1	☐2	☐ times
A Marie Curie nurse?.....	☐1	☐2	☐ times
A Macmillan nurse or other specialist nurse?.....	☐1	☐2	☐ times
Another nurse (*specify*): ☐	☐1	☐2	☐ times
A physiotherapist?.....	☐1	☐2	☐ times
An occupational therapist (OT)?.....	☐1	☐2	☐ times
A psychiatrist?.....	☐1	☐2	☐ times
A psychologist or counsellor?.....	☐1	☐2	☐ times
A spiritual care person or faith leader?..... (for example a chaplain, a rabbi, an imam etc.)	☐1	☐2	☐ times
A social worker?.....	☐1	☐2	☐ times
A palliative care team or 'hospice at home' team?.....	☐1	☐2	☐ times
Other professionals (*specify*):	☐1	☐2	☐ times

☐

4. Please give details of any investigations diagnostic tests you have received over the last 4 months.

Have you had a...	Yes ▼	No ▼	How many times? (*please write down*) ▼
Respiratory function test?	☐1	☐2	☐ times
Chest X-ray?	☐1	☐2	☐ times
Echocardiogram?	☐1	☐2	☐ times
ECG?	☐1	☐2	☐ times
Blood gas test?	☐1	☐2	☐ times
Blood test?	☐1	☐2	☐ times
Magnetic Resonance Image (MRI)?	☐1	☐2	☐ times
CT / CAT scan?	☐1	☐2	☐ times
Other investigations / tests (*please specify):*	☐1	☐2	☐ times

	Yes ▼	No ▼	Usually, how many hours per week? (*please write down*) ▼
5. In the last 4 months, did you have any <u>paid</u> help from a home care worker?	☐1	☐2	☐ hours

6. Did you use any <u>private</u> care in the last 4 months (for example, staying in a private hospital, getting private nurses at home, doing scans or tests privately)?

Yes..... ☐1

No..... ☐2

Please give details:

7. In the past 4 months, because of your illness did you get a **new**	Yes ▼	No ▼
Crutches, walking stick, rollator (tray with wheels on front)?	☐1	☐2
Wheelchair?	☐1	☐2
Oxygen equipment?	☐1	☐2
Feeding pump?	☐1	☐2
Commode?	☐1	☐2
Special bed?	☐1	☐2
Bathroom or toilet adapted?	☐1	☐2
Other equipment *(specify)*?	☐1	☐2

8. In the past 4 months, did family members or friends look after you help take care of you?

Yes..... ☐1

No..... ☐2 → go to Page 17

If yes, how many family members or friends helped?

One person only..... ☐1

Two persons..... ☐2

Three persons..... ☐3

Four persons..... ☐4

Five or more persons..... ☐5

9. Please give details of any help you have received from family members or friends in the last 4 months as a result of your illness. This is family members and friends only (*please add any help from paid carers to question 5).*

This question is particularly important. We realise it is not easy to break this down into hours per week. However it would help a great deal if you could try and remember.

Did you and other friends or family help with…	Yes ▼	No ▼	If yes, usually how many hours per week? *(please write down)* ▼
Personal care? ……. (e.g. washing, dressing)	☐1	☐2	less than 5 hours per week..... ☐1 5-9 hours per week..... ☐2 10-19 hours per week..... ☐3 20-49 hours per week..... ☐4 50 or more hours per week..... ☐5
Medical procedures? ……. (e.g. taking medicines)	☐1	☐2	less than 5 hours per week..... ☐1 5-9 hours per week..... ☐2 10-19 hours per week..... ☐3 20-49 hours per week..... ☐4 50 or more hours per week..... ☐5
Going to appointments or treatments?	☐1	☐2	less than 5 hours per week..... ☐1 5-9 hours per week..... ☐2 10-19 hours per week..... ☐3 20-49 hours per week..... ☐4 50 or more hours per week..... ☐5
Household tasks? ……. (e.g. shopping, cooking)	☐1	☐2	less than 5 hours per week..... ☐1 5-9 hours per week..... ☐2 10-19 hours per week..... ☐3 20-49 hours per week..... ☐4 50 or more hours per week..... ☐5

Did you and other friends or family help with…	Yes ▼	No ▼	If yes, usually how many hours per week? *(please write down)* ▼	
Time spent 'on call'? ..... (e.g. being with you if needed)	☐1	☐2	less than 5 hours per week.....	☐1
			5-9 hours per week.....	☐2
			10-19 hours per week.....	☐3
			20-49 hours per week.....	☐4
			50 or more hours per week.....	☐5
			All the time.....	☐6
Time spent with you? ..... (e.g. visiting, doing things together)	☐1	☐2	less than 5 hours per week.....	☐1
			5-9 hours per week.....	☐2
			10-19 hours per week.....	☐3
			20-49 hours per week.....	☐4
			50 or more hours per week.....	☐5
			All the time.....	☐6

10. Did your family member or friend stop working or reduce work due to your illness in the last 4 months? *(please include paid or unpaid days off work and any carer's leave)*?

Yes.....	☐1	→ How many days did he / she have off work? *(please write down)* ▼
No, he / she is retired.....	☐2	
No, he / she is unemployed.....	☐3	
No, he / she is studying.....	☐4	☐ days
No, he / she carried on working equal hours.....	☐5	

~ ANY OTHER COMMENTS? ~

Please use this page to write down any other comments you might have about the questionnaire. You can leave this page blank if you wish, or attach more pages as needed.

Appendix F.2: Example questionnaire booklet for Caregiver QOL Survey

KING'S College LONDON

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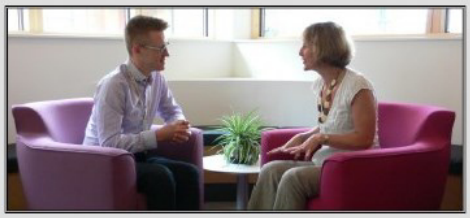
King's College Hospital NHS
NHS Foundation Trust

Professor Irene Higginson BMedSci BMBS FFPHM PhD FRCP, Head of Department
Professor Lynne Turner-Stokes DM FRCP, Herbert Dunhill Chair of Rehabilitation

How does quality of life of people with myeloma change over time?

Questionnaire Booklet for family members / friends of people with Multiple Myeloma



Study Identification Number: ____

Date Questionnaire Completed: ____

Setting Questionnaire Completed: (please tick)

- Hospital Outpatient: ❑
- Hospital Inpatient: ❑
- Home: ❑
- Other: _____

- *This is a research questionnaire. We ask about your views and experiences of caring for your family member or friend who has myeloma.*
- *Please answer all the questions if possible. If you cannot remember, do not know the answer, or are unable to answer a particular question, please write that in.*
- *The final page of this booklet is left blank for you to write down any other comments you might have about the questionnaire.*

Thank you very much. Please feel free to contact me if you have any questions or concerns:

Christina Ramsenthaler *christina.ramsenthaler@kcl.ac.uk* *Tel: 0207 848 5636*

~ Part A : Your family member's / friend's health ~

Please answer the following questions by ticking the box next to the answer that you think most accurately describes how the person you care for has been feeling. It is important to answer all of the questions if possible. Your answers will be used to help improve the care of people with myeloma.
Thank you.

A1) Over the past week, has s/he been affected by pain?

Not at all, no effect - pain was completely controlled ☐0
Slightly – but not bothered to get rid of it ☐1
Moderately – pain limits some activity ☐2
Severely – activities or concentration markedly affected ☐3
Overwhelmingly – unable to think of anything else ☐4

A2) Over the past week, have other symptoms e.g. nausea, coughing or constipation seemed to be affecting how s/he feels?

No, not at all ☐0
Slightly ☐1
Moderately ☐2
Severely ☐3
Overwhelmingly ☐4

A3) Over the past week, has s/he been feeling anxious or worried about their illness or treatment?

No, not at all ☐0
Occasionally ☐1
Sometimes – affects their concentration now and then ☐2
Most of the time – often affects their concentration ☐3
He or she does not seem to think of anything else – completely pre-occupied by worry or anxiety ☐4

A4) Over the past week, have any of his/her family or friends been anxious or worried about him or her?

No, not at all ☐0
Occasionally ☐1
Sometimes – it seems to affect their concentration ☐2
Most of the time ☐3
Yes, they always seem preoccupied with worry ☐4

A5) Over the past week, how much information has been given to him/her, you and his/her family or friends?

- Full information or as much as wanted – always feel free to ask ☐ 0
- Information given but hard to understand ☐ 1
- Information given on request but would have liked more ☐ 2
- Very little given and some questions were avoided ☐ 3
- None at all – when we wanted information ☐ 4

A6) Over the past week, has s/he been able to share how they are feeling with his/her family or friends?

- Yes, as much as they wanted to ☐ 0
- Most of the time ☐ 1
- Sometimes ☐ 2
- Occasionally ☐ 3
- No, not at all with anyone ☐ 4

A7) Over the past week, has s/he been feeling depressed?

- No, not at all ☐ 0
- Occasionally ☐ 1
- Sometimes ☐ 2
- Most of the time ☐ 3
- Yes, all the time ☐ 4

A8) Over the past week, do you think s/he has felt good about themselves?

- Yes, all the time ☐ 0
- Most of the time ☐ 1
- Sometimes ☐ 2
- Occasionally ☐ 3
- No, not at all ☐ 4

A10) Over the past week, how much time do you feel has been wasted on appointments relating to the healthcare of this patient, e.g. waiting around for transport or repeating tests?

- None at all ☐ 0
- Up to half a day wasted ☐ 2
- More than half a day wasted ☐ 4

A11) Over the past week, have any practical matters resulting from his/her illness, either financial or personal, been addressed?

Practical problems have been addressed and their affairs are as up to date as they would wish	☐ 0
Practical problems are in the process of being addressed	☐ 2
Practical problems exist which were not addressed	☐ 4
The patient has had no practical problems	☐ 0

A12) If any, what have been his/her main problems in the past week?

1. .....

2. .....

A13) Please tick which of the following best describes the person you care for:

Fully active	☐ 0
Restricted	☐ 1
Ambulatory	☐ 2
Limited self care	☐ 3
Completely disabled	☐ 4

If you are worried about any of the issues raised on this questionnaire then please speak to your doctor or nurse

~ Part B : Your own health ~

We are interested in some things about you and your health. Please indicate which statements best describe your own health state today. Please answer all of the questions yourself by ticking the box that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

B1) **Mobility**

I have no problems in walking about	❑
I have some problems in walking about	❑
I am confined to bed	❑

B2) **Self-Care**

I have no problems with self-care	❑
I have some problems washing or dressing myself	❑
I am unable to wash or dress myself	❑

B3) **Usual Activities** *(e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities	❑
I have some problems with performing my usual activities	❑
I am unable to perform my usual activities	❑

B4) **Pain/Discomfort**

I have no pain or discomfort	❑
I have moderate pain or discomfort	❑
I have extreme pain or discomfort	❑

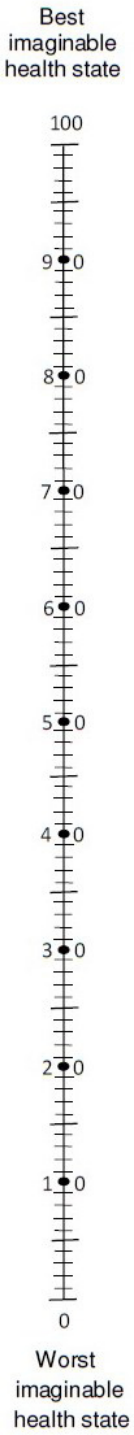
B5) **Anxiety/Depression**

I am not anxious or depressed	❑
I am moderately anxious or depressed	❑
I am extremely anxious or depressed	❑

B6) *To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.*

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



~ Part C : Your feelings ~

Following are a few statements about how you might feel. Please tick the box that best describes how you feel.

	Never	Rarely	Sometimes	Quite frequently	Nearly always
C1) Do you feel that because of the time you spend with your relative that you don't have enough time for yourself?	0 ❑	1 ❑	2 ❑	3 ❑	4 ❑
C2) Do you feel stressed between caring for your relative and trying to meet other responsibilities (work/family)?	0 ❑	1 ❑	2 ❑	3 ❑	4 ❑
C3) Do you feel angry when you are around your relative?	0 ❑	1 ❑	2 ❑	3 ❑	4 ❑
C4) Do you feel that your relative currently affects your relationship with family members or friends in a negative way?	0 ❑	1 ❑	2 ❑	3 ❑	4 ❑
C5) Do you feel strained when you are around your relative?	0 ❑	1 ❑	2 ❑	3 ❑	4 ❑
C6) Do you feel that your health has suffered because of your involvement with your relative?	0 ❑	1 ❑	2 ❑	3 ❑	4 ❑
C7) Do you feel that you don't have as much privacy as you would like because of your relative?	0 ❑	1 ❑	2 ❑	3 ❑	4 ❑
C8) Do you feel that your social life has suffered because you are caring for your relative?	0 ❑	1 ❑	2 ❑	3 ❑	4 ❑
C9) Do you feel that you have lost control of your life since your relative's illness?	0 ❑	1 ❑	2 ❑	3 ❑	4 ❑
C10) Do you feel uncertain what to do about your relative?	0 ❑	1 ❑	2 ❑	3 ❑	4 ❑
C11) Do you feel you should be doing more for your relative?	0 ❑	1 ❑	2 ❑	3 ❑	4 ❑
C12) Do you feel you should do a better job in caring for your relative?	0 ❑	1 ❑	2 ❑	3 ❑	4 ❑

~ ANY OTHER COMMENTS? ~

Please use this page to write down any other comments you might have about the questionnaire. You can leave this page blank if you wish, or attach more pages as needed.